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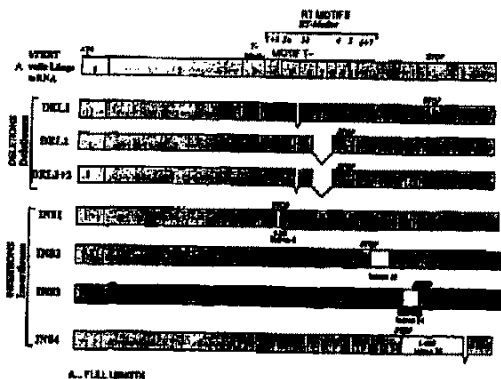
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(54) **SEQUENCES D'ADN REGULATRICES DU GENE DE LA SOUS-UNITE TELOMERASE CATALYTIQUE
HUMAINE ET LEUR UTILISATION A DES FINS DIAGNOSTIQUES ET THERAPEUTIQUES**
(54) **REGULATORY DNA SEQUENCES OF THE HUMAN CATALYTIC TELOMERASE SUB-UNIT GENE,
DIAGNOSTIC AND THERAPEUTIC USE THEREOF**

(57)

The present invention relates to regulatory DNA sequences containing promotor sequences, in addition to intervening sequences, for the human catalytic telomerase sub-unit gene. The invention also relates to the use of said DNA sequences for pharmaceutical, diagnostic and therapeutic purposes, especially in the treatment of cancer and ageing.





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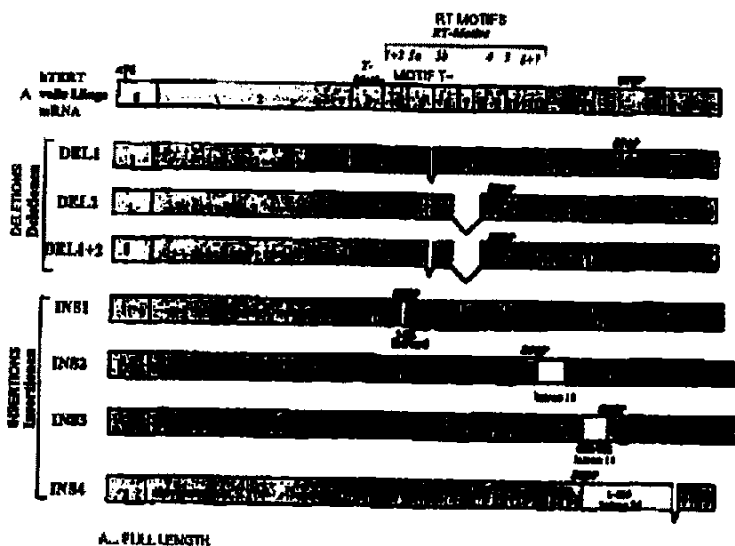
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(54) **SEQUENCES D'ADN REGULATRICES DU GENE DE LA
SOUS-UNITE TELOMERASE CATALYTIQUE HUMAINE
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ET THERAPEUTIQUES**

(54) **REGULATORY DNA SEQUENCES OF THE HUMAN
CATALYTIC TELOMERASE SUB-UNIT GENE, DIAGNOSTIC
AND THERAPEUTIC USE THEREOF**



(57) L'invention concerne des séquences d'ADN régulatrices, contenant des séquences promoteurs, ainsi que des séquences interposées, pour le gène de la sous-unité télomérase catalytique humaine. L'invention concerne en outre l'utilisation de ces séquences d'ADN à des fins pharmaceutiques, diagnostiques et thérapeutiques, avant tout pour traiter le cancer et le vieillissement.

(57) The present invention relates to regulatory DNA sequences containing promotor sequences, in addition to intervening sequences, for the human catalytic telomerase sub-unit gene. The invention also relates to the use of said DNA sequences for pharmaceutical, diagnostic and therapeutic purposes, especially in the treatment of cancer and ageing.





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<p>(21) Internationales Aktenzeichen: PCT/EP98/08216</p> <p>(22) Internationales Anmeldedatum: 22. Dezember 1998 (22.12.98)</p> <p>(30) Prioritätsdaten: 197 57 984.1 24. Dezember 1997 (24.12.97) DE</p> <p>(71) Anmelder (für alle Bestimmungsstaaten ausser US): BAYER AKTIENGESELLSCHAFT [DE/DE]; D-51368 Leverkusen (DE).</p> <p>(72) Erfinder; und (75) Erfinder/Anmelder (nur für US): HAGEN, Gustav [DE/DE]; Bertha-von-Suttner-Strasse 31, D-51373 Leverkusen (DE). WICK, Maresa [DE/DE]; Andreas-Gryphius-Strasse 26, D-51065 Köln (DE). ZUBOV, Dmitry [RU/DE]; Roggen-dorfstrasse 59, D-51061 Köln (DE).</p> <p>(74) Gemeinsamer Vertreter: BAYER AKTIENGESELLSCHAFT; D-51368 Leverkusen (DE).</p>	<p>(81) Bestimmungsstaaten: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO Patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), eurasisches Patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), europäisches Patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI Patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).</p> <p>Veröffentlicht <i>Ohne internationalen Recherchenbericht und erneut zu veröffentlichen nach Erhalt des Berichts.</i></p>	
<p>(54) Title: REGULATORY DNA SEQUENCES OF THE HUMAN CATALYTIC TELOMERASE SUB-UNIT GENE, DIAGNOSTIC AND THERAPEUTIC USE THEREOF</p> <p>(54) Bezeichnung: REGULATORISCHE DNA-SEQUENZEN DES GENS DER HUMANEN KATALYTISCHEN TELOMERASE-UNTEREINHEIT UND DEREN DIAGNOSTISCHE UND THERAPEUTISCHE VERWENDUNG</p>		
<p style="text-align: center;">A. FULL LENGTH</p>		
<p>(57) Abstract</p> <p>The present invention relates to regulatory DNA sequences containing promoter sequences, in addition to intervening sequences, for the human catalytic telomerase sub-unit gene. The invention also relates to the use of said DNA sequences for pharmaceutical, diagnostic and therapeutic purposes, especially in the treatment of cancer and ageing.</p>		

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Regulatory DNA sequences of the gene for the human catalytic telomerase subunit, and their diagnostic and therapeutic use

Structure and function of the chromosome ends

5

The genetic material of eukaryotic cells is distributed on linear chromosomes. The ends of hereditary units are termed telomeres, derived from the Greek words *telos* (end) and *meros* (part, segment). Most telomeres consist of repeats of short sequences which are mainly composed of thymine and guanine (Zakian, 1995). In all the
10 vertebrates which have so far been investigated, the telomeres consist of the sequence TTAGGG (Meyne *et al.*, 1989).

The telomeres have a variety of important functions. They prevent the fusion of chromosomes (McClintock, 1941) and thus the formation of dicentric hereditary
15 units. Such chromosomes having two centromeres can lead to the development of cancer due to loss of heterozygosis or duplication, or loss of genes.

In addition, telomeres serve the purpose of distinguishing intact hereditary units from damaged hereditary units. Thus, yeast cells ceased their cell division when they
20 contained a chromosome without a telomere (Sandell and Zakian, 1993).

Telomeres fulfil another important task in association with the replication of eukaryotic cell DNA. In contrast to the circular genomes of prokaryotes, the linear chromosomes of eukaryotes cannot be completely replicated by the DNA polymerase
25 complex. RNA primers are required to initiate DNA replication. After elimination of the RNA primers, extension of the Okazaki fragments and subsequent ligation, the newly synthesized DNA strand lacks the 5' end since the RNA primer cannot be replaced by DNA at that point. Without special protective mechanisms, the chromosomes would therefore shrink with each cell division ("end-replication
30 problem"; Harley *et al.*, 1990). The non-coding telomere sequences presumably constitute a buffer zone for preventing the loss of genes (Sandell and Zakian, 1993).

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In addition to this, telomeres also play an import role in regulating cell ageing (Olovnikov, 1973). Human somatic cells exhibit a limited capacity for replication in culture; after a certain period of time, they become senescent. In this state, the cells no longer divide even after having been stimulated with growth factors; however,
5 they do not die and remain metabolically active (Goldstein, 1990). Various observations support the hypothesis that a cell determines how many more times it can divide on the basis of the length of its telomeres (Allsopp *et al.*, 1992).

In summary, the telomeres consequently possess key functions in the ageing of cells,
10 and in stabilizing the genetic material and preventing cancer.

The enzyme telomerase synthesizes the telomeres

As described above, organisms which possess linear chromosomes can only replicate
15 their genome incompletely in the absence of a special protective mechanism. Most eukaryotes use a special enzyme, i.e. telomerase, for regenerating the telomere sequences. Telomerase is expressed constitutively in the single-cell organisms which have so far been investigated. On the other hand, telomerase activity has only been measured in humans in germ cells and tumour cells, whereas neighbouring somatic
20 tissue did not contain any telomerase (Kim *et al.*, 1994).

Telomerase can also be designated functionally as terminal telomere transferase, which is located in the cell nucleus as a multiprotein complex. While the RNA moiety of human telomerase has been known for a relatively long period of time
25 (Feng *et al.*, 1995), the catalytic subunit of this enzyme group was recently identified in a variety of organisms (Lingner *et al.*, 1997; cf. our application PCT EP/98/03468 which is likewise pending). These catalytic subunits of telomerase are strikingly homologous both among themselves and in relation to all previously known reverse transcriptases.

30

WO 98/14592 also describes nucleic acid and amino acid sequences of the catalytic telomerase subunit.

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Activation of telomerase in human tumours

5 It was originally only possible to demonstrate telomerase activity in humans in germ
line cells and not in normal somatic cells (Hastie *et al.*, 1990; Kim *et al.*, 1994).
Following the development of a more sensitive detection method (Kim *et al.*, 1994),
a low telomerase activity was also detected in hematopoietic cells (Broccoli *et al.*,
1995; Counter *et al.*, 1995; Hiyama *et al.*, 1995). It is true, however, that these cells
10 nevertheless exhibited a reduction in the telomeres (Vaziri *et al.*, 1994; Counter *et al.*, 1995). It has still not been resolved whether the quantity of enzyme in these cells
is not sufficient for compensating the telomere loss or whether the telomerase activity
which is measured stems from a subpopulation, e.g. incompletely differentiated
CD34⁺38⁺ precursor cells (Hiyama *et al.*, 1995). In order to resolve this, it would be
necessary to detect telomerase activity in a single cell.

15 Interestingly, however, significant telomerase activity was detected in a large number
of the tumour tissues which had thus far been tested (1734/2031, 85%; Shay, 1997),
whereas no activity was found in normal somatic tissue (1/196, <1%, Shay, 1997). In
addition various investigations have shown that the telomeres still shrank in
20 senescent cells which were transformed with viral oncoproteins and it was only
possible to detect telomerase in the subpopulation which survived the growth crisis
(Counter *et al.*, 1992). The telomeres were also stable in these immortalized cells.
(Counter *et al.*, 1992). Similar findings from investigations in mice (Blasco *et al.*,
1996) support the assumption that reactivation of the telomerase is a late event in
25 tumorigenesis.

Based on these results, a "telomerase hypothesis" was developed which links the loss
of telomere sequences and cell ageing with telomerase activity and the development
of cancer. In long-lived species such as humans, the shrinking of the telomeres can be
30 regarded as being a mechanism for suppressing tumours. Differentiated cells which
do not contain any telomerase cease their cell division at a particular telomere length.
If such a cell mutates, it can only form a tumour if the cell can extend its telomeres.

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Otherwise, the cell would continue to lose telomere sequences until its chromosomes became unstable and it was finally destroyed. Telomerase reactivation is presumably the main mechanism used by tumour cells to stabilize their telomeres.

5 It follows from these observations and considerations that it should be possible to treat tumours by inhibiting the telomerase. Conventional cancer therapies using cytostatic agents or short-wave radiation damage all the dividing cells in the body in addition to the tumour cells. However, since only germ line cells, apart from tumour cells, contain significant telomerase activity, telomerase inhibitors would attack the
10 tumour cells more specifically and consequently elicit fewer undesirable side effects. Telomerase activity has been detected in all the tumour tissues which have so far been tested, which means that these therapeutic agents could be employed against all types of cancer. The effect of telomerase inhibitors would then set in when the telomeres of the cells had shortened to such an extent that the genome became
15 unstable. Since tumour cells usually possess telomeres which are shorter than those of normal somatic cells, cancer cells would be the first to be eliminated by the telomerase inhibitors. By contrast, cells possessing long telomeres, such as the germ cells, would only be damaged at a much later date. Telomerase inhibitors consequently represent a potential way forward in the treatment of cancer.

20 It becomes possible to obtain unambiguous answers to the question of the nature and points of attack of physiological telomerase inhibitors once the manner in which expression of the telomerase gene is regulated has also been identified.

25 Regulation of gene expression in eukaryotes

There are a large number of points in eukaryotic gene expression, i.e. the cellular flow of information from the DNA to the protein by way of the RNA, at which regulatory mechanisms can exert an effect. Examples of individual control steps are
30 gene amplification, the recombination of gene loci, chromatin structure, DNA methylation, transcription, post-transcriptional modifications of mRNA, mRNA transport, translation and post-translational modifications of proteins. Studies which

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have been carried out to date indicate that control at the level of transcription initiation is of the greatest importance (Latchman, 1991).

5 A region which is responsible for regulating transcription, and which is designated the promoter region, is located directly upstream of the transcription start of a gene which is transcribed by RNA polymerase II. Comparison of the nucleotide sequences of promoter regions from a large number of known genes shows that particular sequence motifs occur regularly in this region. These elements include, inter alia, the TATA box, the CCAAT box and the GC box, which elements are recognized by
10 specific proteins. The TATA box, which is located about 30 nucleotides upstream of the transcription start, is, for example, recognized by the TFIID subunit TBP ("TATA box-binding protein"), whereas particular GC-rich sequence segments are specifically bound by the transcription factor Sp1 ("specificity protein1").

15 The promoter can be functionally subdivided into a regulatory segment and a constitutive segment (Latchman, 1991). The constitutive control region comprises the so-called core promoter which enables transcription to be initiated correctly. This promoter contains the sequence elements which are described as UPE's (upstream promoter elements) which are necessary for efficient transcription. The regulatory
20 control segments, which can be interlaced with the UPE's, possess sequence elements which can be involved in the signal-dependent regulation of transcription by hormones, growth factors, etc. They impart tissue-specific or cell-specific promoter properties.

25 DNA segments which are able to exert an influence on gene expression over relatively large distances are a characteristic feature of eukaryotic genes. These elements can be located upstream or downstream of a transcription unit, or within the unit, and can perform their function independently of their orientation. These sequence segments may reinforce (enhancers) or attenuate (silencers) promoter
30 activity. In a similar way to the promoter regions, enhancers and silencers also accommodate several binding sites for transcription factors.

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The invention relates to the DNA sequences from the 5'-flanking region of the gene for the catalytically active human telomerase subunit and intron sequences for this gene.

- 5 The invention particularly relates to the 5'-flanking regulatory DNA sequence which contains the promoter DNA sequence for the gene for the human catalytic telomerase subunit, as depicted in Fig. 10 (SEQ ID NO 3).

10 The invention furthermore relates to part regions of the 5'-flanking regulatory DNA sequence, as depicted in Fig. 4 (SEQ ID NO 1), which has a regulatory effect.

15 Intron sequences for the gene for the human catalytic telomerase subunit, in particular those sequences which have a regulatory effect, are also part of the subject-matter of the present invention. The intron sequences according to the invention are described in detail in the context of Example 5 (cf. SEQ ID NO 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19 and 20).

20 The invention furthermore relates to a recombinant construct which comprises the DNA sequences according to the invention, in particular the 5'-flanking DNA sequence of the gene for the human catalytic telomerase subunit, or part regions thereof.

25 Preference is given to recombinant constructs which, in addition to the DNA sequences according to the invention, in particular the 5'-flanking DNA sequence of the gene for the human catalytic telomerase subunit, or part regions thereof, also contain one or more additional DNA sequences which encode polypeptides or proteins.

30 According to a particularly preferred embodiment, these additional DNA sequences encode antineoplastic proteins.

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Particular preference is given to those antineoplastic proteins which inhibit angiogenesis directly or indirectly. Examples of these proteins are:

5 Plasminogen activator inhibitor (PAI-1), PAI-2, PAI-3, angiostatin, endostatin, platelet factor 4, TIMP-1, TIMP-2, TIMP-3 and leukaemia inhibitory factor (LIF).

Antineoplastic proteins which have a direct or indirect cytostatic effect on tumours are likewise particularly preferred. These proteins include, in particular:

10 perforin, granzyme, IL-2, IL-4, IL-12, interferons, such as IFN- α , IFN- β and IFN- γ , TNF, TNF- α , TNF- β , oncostatin M; tumour suppressor genes, such as p53, retinoblastoma.

15 Particular preference is furthermore given to antineoplastic proteins which, where appropriate in addition to their antineoplastic effect, stimulate inflammations and thereby contribute to the elimination of tumour cells. Examples of these proteins are:

20 RANTES, monocyte chemotactic and activating factor (MCAF), IL-8, macrophage inflammatory protein (MIP-1 α , - β), neutrophil activating protein-2 (NAP-2), IL-3, IL-5, human leukaemia inhibitory factor (LIF), IL-7, IL-11, IL-13, GM-CSF, G-CSF and M-CSF.

25 Particular preference is furthermore given to antineoplastic proteins which, due to their action as enzymes, are able to convert precursors of an antineoplastic active compound into an antineoplastic active compound. Examples of these enzymes are:

30 herpes simplex virus thymidine kinase, varicella zoster virus thymidine kinase, bacterial nitroreductase, bacterial β -glucuronidase, plant β -glucuronidase from *Secale cereale*, human glucuronidase, human carboxypeptidase, bacterial carboxypeptidase, bacterial β -lactamase, bacterial cytosine deaminidase, human catalase and/or phosphatase, human alkaline phosphatase, type 5 acid phosphatase, human

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lysooxidase, human acid D-aminooxidase, human glutathione peroxidase, human eosinophil peroxidase and human thyroid peroxidase.

5 The abovementioned recombinant constructs can also contain DNA sequences which encode factor VIII or factor IX, or part fragments thereof. These DNA sequences also include other blood clotting factors.

The abovementioned recombinant constructs can also contain DNA sequences which encode a reporter protein. Examples of these reporter proteins are:

10 Chloramphenicol acetyl transferase (CAT), glow-worm luciferase (LUC), β -galactosidase (β -Gal), secreted alkaline phosphatase (SEAP), human growth hormone (hGH), β -glucuronidase (GUS), green-fluorescing protein (GFP), and all the variants derived therefrom, aquarin and obelin.

15 Recombinant constructs according to the invention can also contain DNA which encodes the human catalytic telomerase subunit and its variants and fragments in the antisense orientation. Where appropriate, these constructs can also contain other protein subunits of the human telomerase and the telomerase RNA component in the
20 antisense orientation.

The recombinant constructs can, in addition to the DNA which encodes the human catalytic telomerase subunit, and its variants and fragments, also contain other protein subunits of the human telomerase and the telomerase RNA component.

25 The invention furthermore relates to a vector which contains the abovementioned DNA sequences according to the invention, in particular the 5'-flanking DNA sequences and also one or more of the other DNA sequences mentioned above.

30 The preferred vector for these constructs is a virus, for example a retrovirus, an adenovirus, an adeno-associated virus, a herpes simplex virus, a vaccina virus, a lentiviral virus, a Sindbis virus and a Semliki forest virus.

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Preference is also given to using plasmids as vectors.

5 The invention furthermore relates to pharmaceutical preparations which comprise recombinant constructs or vectors according to the invention; for example a preparation in a colloidal dispersion system.

10 Examples of suitable colloidal dispersion systems are liposomes or polylysine ligands.

The preparations of the constructs or vectors according to the invention in colloidal dispersion systems can be supplemented with a ligand which binds to the membrane structures of tumour cells. Such a ligand can, for example, be attached to the construct or the vector or else be a component of the liposome structure.

15 Suitable ligands are, in particular, polyclonal or monoclonal antibodies, or antibody fragments thereof, which bind, by their variable domains, to the membrane structures of tumour cells, or substances carrying mannose terminally, cytokines or growth factors, or fragments or part sequences thereof, which bind to receptors on tumour cells.

20 Examples of corresponding membrane structures are receptors for a cytokine or a growth factor, such as IL-1, EGF, PDGF, VEGF, TGF β , insulin or insulin-like growth factor (IGF), or adhesion molecules, such as SLeX, LFA-1, MAC-1, 25 LECAM-1 or VLA-4, or the mannose-6-phosphate receptor.

The present invention includes pharmaceutical preparations which, in addition to the vector constructs according to the invention, can also comprise non-toxic, inert, pharmaceutically suitable excipients. It is possible to conceive of administering (e.g. 30 intravenously, intraarterially, intramuscularly, subcutaneously, intradermally, anally, vaginally, nasally, transdermally, intraperitoneally, as an aerosol or orally) these preparations at the site of a tumour or administering them systemically.

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The vector constructs according to the invention can be employed in gene therapy.

5 The invention furthermore relates to a recombinant host cell, in particular a recombinant eukaryotic host cell, which harbours the above-described constructs or vectors.

10 The invention furthermore relates to a process for identifying substances which affect the promoter activity, silencer activity or enhancer activity of the catalytic telomerase subunit, with this process comprising the following steps:

15 A. adding a candidate substance to a host cell which harbours the regulatory DNA sequence according to the invention, in particular the 5'-flanking regulatory DNA sequence for the gene for the human catalytic telomerase subunit, or a part region thereof which has a regulatory effect, which sequence or part region is functionally linked to a reporter gene, and

B. measuring the effect of the substance on expression of the reporter gene.

20 The process can be employed for identifying substances which increase the promoter activity, silencer activity or enhancer activity of the catalytic telomerase subunit.

25 The process can furthermore be employed for identifying substances which inhibit the promoter activity, silencer activity or enhancer activator of the catalytic telomerase subunit.

30 The invention furthermore relates to a process for identifying factors which bind specifically to fragments of the DNA fragments according to the invention, in particular the 5'-flanking regulatory DNA sequence of the catalytic telomerase subunit. This method comprises screening an expression cDNA library using the above-described DNA sequence, or subfragments of widely differing length, as the probe.

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The above-described constructs or vectors can also be used for preparing transgenic animals.

5 The invention furthermore relates to a process for detecting telomerase-associated conditions in a patient, which process comprises the following steps:

10 A. incubating a construct or vector, which contains the DNA sequence according to the invention, in particular the 5'-flanking regulatory DNA sequence for the gene for the human catalytic telomerase subunit, or a part region thereof having a regulatory effect, and a reporter gene, with body fluids or cell samples,

15 B. detecting the activity of the reporter gene in order to obtain a diagnostic value; and

C. comparing the diagnostic value with standard values for the reporter gene construct in standardized normal cells or body fluids of the same type as the test sample;

20

The detection of diagnostic values which are higher or lower than the standard comparative values indicates a telomerase-associated condition, which in turn indicates a pathogenic condition.

25 Explanation of the figures:

Fig. 1: Southern blot analysis using genomic DNA from various species

30 A: Photograph of an ethidium bromide-stained 0.7% agarose gel containing approximately 4 µg of Eco RI-cut genomic DNA. Track 1 contains Hind III-cut λ DNA as size markers (23.5, 9.4, 6.7, 4.4, 2.3, 2.0 and 0.6 kb). Tracks 2 to 10 contain human, rhesus monkey, Sprague

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Dawley rat, BALB/c mouse, dog, bovine, rabbit, chicken and yeast (*Saccharomyces cerevisiae*) genomic DNA.

5 B: Autoradiogram, corresponding to Fig.1 A, of a Southern blot analysis in which radioactively labelled hTC-cDNA probe of about 720 bp in length is used for the hybridization.

Fig. 2: Restriction analysis of the recombinant λ DNA of the phage clone P12, which hybridizes with a probe from the 5' region of the hTC cDNA.

10 The figure shows a photograph of an ethidium bromide-stained 0.4% agarose gel. Tracks 1 and 2 contain Eco RI/Hind III-cut λ DNA and a 1 kb ladder from Gibco as size markers. Tracks 3 - 7 each contain 250 ng of the DNA from the recombinant phage which has been cut with Bam HI (track 3), Eco RI (track 4), Sal I (track 5), Xho I (track 6) and Sac I (track 7). The arrows mark the two λ arms of the vector EMBL3 Sp6/T7.

Fig. 3: Restriction analysis and Southern blot analysis of the recombinant λ DNA of the phage clone which hybridizes with a probe from the 5' region of the hTC cDNA.

20 A: The figure shows a photograph of an ethidium bromide-stained 0.8% agarose gel. Tracks 1 and 15 contain a 1 kb ladder from Gibco as size markers. Tracks 2 to 14 each contain 250 ng of cut λ DNA from the recombinant phage clone. The following enzymes were employed: track 2: Sac I, track 3: Xho I, track 4: Xho I, Xba I, track 5: Sac I, Xho I, track 25 6: Sal I, Xho I, Xba I, track 7: Sac I, Xho I, Xba I, track 8: Sac I, Sal I, Xba I, track 9: Sac I, Sal I, BamH I, track 10: Sac I, Sal I, Xho I, track 11: Not I, track 12: Sma I, track 13: empty, track 14: not digested.

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B: Autoradiogram, corresponding to Fig. 3 A, of a Southern blot analysis. A 5'-hTC cDNA fragment of about 420 bp in length was used as the probe for the hybridization.

5 Fig. 4: Partial DNA sequence of the 5'-flanking region and of the promoter of the gene for the human catalytic telomerase subunit. The ATG start codon in the sequence is printed in bold. The depicted sequence corresponds to SEQ ID NO 1.

10 Fig. 5: Use of primer extension analysis to identify the transcription start.

The figure shows an autoradiogram of a denaturing polyacrylamide gel which was selected for depicting a primer extension analysis. An oligonucleotide having the sequence
 15 5'GTAAAGTTGTAGCTTACACTGGTTCTC 3' was used as the primer. The primer extension reaction was loaded in track 1. Tracks G, A, T and C constitute the sequence reactions using the same primer and the corresponding dideoxynucleotides. The thick arrow marks the main transcription start while the thin arrows point to three subsidiary
 20 transcription start points.

Fig. 6: cDNA sequence of the human catalytic telomerase subunit (hTC; cf. our pending application PCT/EP/98/03468). The depicted sequence corresponds to SEQ ID NO 2.

25

Fig. 7: Structural organization and restriction map of the human hTC gene and its 5'-flanking and 3'-flanking regions.

30

Exons are shown as consecutively numbered rectangles which are filled-in in black, and introns are shown as regions which are not filled in. Untranslated sequence segments in the exons are hatched. Translation starts in exon 1 and ends in exon 16. Restriction enzyme cleavage sites

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are marked as follows: S, SacI; X, XhoI. The relative arrangement of the five phage clones (P2, P3, P5, P12, P17), and of the product from the genome walking, are shown by thin lines. As the dots indicate, the sequence of intron 16 has only been partly deciphered.

5

Fig. 8: HTL splice variants.

10

15

A: Diagrammatic structure of the hTC mRNA splice variants. The complete hTC mRNA is depicted as a rectangle with a grey background in the upper region of the figure. The 16 exons are depicted in accordance with their size. The translation start (ATG) and the stop codon, and also the telomerase-specific T motif, and the seven RT motifs, are all shown. The hTC variants are subdivided into deletion and insertion variants. The missing exon sequences are marked in the deletions. The insertions are shown by additional white rectangles. The sizes and origins of the inserted sequences are given. Newly formed stop codons are marked. The size of the insertion in variant INS2 is unknown.

20

25

Fig. 9: Identification of the transcription start by means of RT-PCR analysis.

30

The RT-PCR was carried out using a cDNA library prepared from HL 60 cells and genomic DNA as the positive control. A common 3' primer hybridizes to a region of the exon 1 sequence. The positions of the different 5' primers in the coding region or the 5'-flanking region are given. In the negative control, no template DNA was added to the PCR reaction. M: DNA size marker.

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Fig. 10: Nucleotide sequence and structural features of the hTC promoter.

5 The figure depicts 11273 bp of the 5'-flanking hTC gene sequence, beginning with the translation start codon ATG (+1). The putative region of the translation start is underlined. Possible regulatory sequence segments within the 4000 bp upstream of the translation start are ringed. The depicted sequence corresponds to SEQ ID NO 3.

Fig. 11: Activity of the hTC promoter in HEK-293 cells.

10 The first 5000 bp of the 5'-flanking hTC gene region are shown diagrammatically in the upper part of the figure. The ATG start codon is picked out. CpG-rich islands are marked by grey rectangles. The sizes of the hTC promoter-luciferase construct are shown on the left-hand side of the figure. The promoterless pGL2 basic construct and the SV40
15 promoter construct pGL2-Pro were used as controls in each transfection. The relative luciferase activities of the different promoter constructs in HEK cells are shown as continuous bars on the right-hand side of the figure. The standard deviation is indicated. The numerical values represent the average of two independent experiments which were carried
20 out in duplicate.

Tab. 1: Exon-intron transitions in the hTC gene

25 The table lists the nucleotide sequences at the 3' and 5' splice transitions of the hTC gene. The consensus sequences for donor and acceptor sequences (AG and GT) are underlaid with grey rectangles. The table shows the intron sequences (small letters) and exon sequences (large letters) which flank the splice acceptor and donor sites. The sizes of the exons and introns are given in bp.

30 Tab. 2: Potential binding sites for DNA-binding factors in the nucleotide sequence of intron 2

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5

The search for possible DNA-binding factors (e.g. transcription factors) was carried out using the "find pattern" algorithm from the Genetics Computer Group (Madison, USA) GCG sequence analysis program package. The table lists the abbreviations of the DNA-binding factors which were identified and their location in intron 2.

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Tab. 1

3' Acceptor Sequence			5' Donor Sequence		
Intron	Exon	Exon No.	Exon	Intron	Intron No.
bp	bp		bp	bp	
5' flanking region	GTTCAGGCAGCGCTGCGT	1	CGCCCCCTCCTTCGCCAG	gtgggccccccggggtcg	1
caggcgcttcccccgag	GTCTCCTGCCCTCAAGGAGC	2	TGGCTGCCGAGGAGCCCCAG	gtgaggaggtgtgtggcgt	2
catgtctctctctttttag	GGGTGGCTGTGTTCGGGC	3	TGCAAAAGCAATTGGAATCAG	gtactgtatacccccaagcca	3
gaggggtctctctatgttag	ACACCACCTTGAGAGGGTG	4	GTTCGGCAGAGAAAAGAGG	gtgctgtgtctttgtttta	4
cccatgtgtcccccgtag	GCCGAGCGTCTCACCTCGA	5	TCAGCTGTACTTTTGTCAAG	gtgggtgccgggggaacccc	5
ctcgctcccaactcacatag	GTGGATGTGACGGGGCGGT	6	CAAGGCCTTCAGAGCCAC	gttaggttcaactgtgtgata	6
ccctctctctgtccggtag	GTCTCTACCTTGACAGACC	7	TCGCGTCTGCATCGAGCAG	gtttggggcaactgcccgtca	7
ctcccgctgtctttcttag	AGCTCCTCCCTGAATGAGG	8	CCGTGGGCATCAGGGGCAA	gttagtcaaggtggccaggt	8
ctgtgtcttccccgcccag	GTCTACGTCCAGTGCCAG	9	CGGGGATTCCGGGGACGG	gttagggcctctcttcccc	9
gtattttcccttatttttag	GCTGCTCCTGCGTTTGGTG	10	ACGGGAAAACCTTCTCTCAG	gttagggccctgtccgtgtg	10
cattgccccctgtgcttag	GACCTGGTCCGAGGTGTC	11	TCGAGAGCGACTACTCCAG	gttagcgcaactggccgga	11
attccccctgtgtcttag	CTATGCCCCGACCTCCATC	12	CCTGTTTCTGCAATTGTCAG	gttagcaggctgatgtgtoa	12
tctttcttggcgactcttag	GTGAACAGCCTCCAGACGG	13	TCCTGCTGCAGCGGTACAG	gttagcccgcccaagggg	13
ctgtccggccatctctcttag	GTTTCAGGCATGTGTCTG	14	CTGAAAGCCCAAGAACCCAG	gtatgtgcaggtgccttggc	14
agcctctgttttccccctag	GGATGTGCTGGGGGCCAA	15	CTGGGTCCTACTCAGGACAG	gcaagtggtggggaggcc	15
tctgatttttggcccccgtag	CCCAGACCGAGCTGAGTCG	16	TTTTTCAGTTTGAATAAA	3' flanking region	

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Tab. 2

Factors	Location in intron 2
C/EBP	2925
CRE.2	2749
Sp1	2378, 4094, 4526, 4787, 4835, 4995
AP-2 CS3	5099
AP-2 CS4	2213, 3699, 4667, 5878, 5938, 6059, 6180, 6496
AP-2 CS5	5350, 5798, 5880, 5940, 6061, 6182, 6375, 6498
PEA3	934, 2505
P53	2125
GR uteroglobin	848, 1487, 2956
PR uteroglobin	3331
Zeste-white	1577, 1619, 1703, 1745, 1787, 1829, 1871, 1913, 1955, 1997, 2039, 2081, 3518, 3709, 4765, 5014, 5055
GRE	846
MyoD-MCK right site/rev	447, 509, 558, 1370, 1595, 1900, 2028, 2099, 4557
MyoD-MCK left site	108, 118, 453, 1566, 1608, 1692, 1734, 1818, 1902, 1986, 2372, 2460, 2720, 3491, 5030
Ets-1 CS	6408
API	3784, 4406
CREB	2801
GATA-1	839, 1390, 3154
c-Myc	108, 118, 453, 1566, 1608, 1692, 1734, 1818, 1902, 1986, 2372, 2460, 2720, 3491, 5030
CACCC site	991
CCAAT site	1224
CCAC box	992
CAAT site	463, 2395
Rb site	992, 4663
TATA	3650
CDEI	106, 1564, 1606, 1690, 1732, 1816, 1900, 1984

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Examples

The human gene for the catalytic telomerase subunit (ghTC), and the regions of this gene located 5' and 3', were cloned, while the start point for transcription was determined, potential binding sites for DNA-binding proteins were identified and active promoter fragments were highlighted. The sequence of the hTC cDNA (Fig. 6) has already been reported in our application PCT/EP/98/03468, which is also pending. Unless otherwise mentioned, all the data refer to the position of the cDNA in this sequence.

Example 1

A genomic Southern blot analysis was used to determine whether ghTC constitutes a single gene in the human genome or whether there exist several loci for the hTC gene and possibly also ghTC pseudogenes.

In order to do this, a commercially available zoo blot from Clontech was subjected to Southern blot analysis. This blot contains 4 µg of Eco RI-cut genomic DNA from nine different species (human, monkey, rat, mouse, dog, bovine, rabbit, chicken and yeast). With the exception of yeast, chicken and human, the DNA was isolated from kidney tissue. The human genomic DNA was isolated from placenta and the chicken genomic DNA was purified from liver tissue. An hTC cDNA fragment of about 720 bp in length, which was isolated from hTC cDNA, variant Del2 (position 1685 to 2349 plus 2531 to 2590 in Fig. 6 [deletion 2; cf. Example 5 in Fig. 8]), was used as the radioactively labelled probe in the autoradiogram in Fig. 1. The experimental conditions for the blot hybridization and washing steps were taken from Ausubel *et al.* (1987).

In the case of the human DNA, the probe recognizes two specific DNA fragments. The smaller Eco RI fragment, of from about 1.5 to 1.8 kb in length, probably originates from two Eco RI cleavage sites in an intron in the ghTC DNA. On the

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basis of this result, it is to be assumed that only one single ghTC gene is present in the human genome.

Example 2

5

In order to isolate the 5' flanking hTC gene sequence, approx. 1.5×10^6 phages from a human genomic placenta gene library (EMBL 3 SP6/T7 from Clontech, order number HL1067j) were hybridized on nitrocellulose filters (0.45 μ m; from Schleicher and Schuell), in accordance with the manufacturer's instructions, with a
10 radioactively labelled 5'-hTC cDNA fragment of about 500 bp in length (position 839 to 1345 in Fig. 6). The nitrocellulose filters were firstly incubated, at 42°C for two hours, in 2 x SSC (0.3 M NaCl; 0.5 M Tris-HCl, pH 8.0) and then in a prehybridization solution (50% formamide; 5 x SSPE, pH 7.4; 5 x Denhard's solution; 0.25% SDS; 100 μ g of herring sperm DNA/ml). For the overnight
15 hybridization, the prehybridization solution was supplemented with 1.5×10^6 cpm of denatured, radioactively labelled probe/ml of solution. Nonspecifically bound radioactive DNA was removed under stringent conditions, i.e. by means of three five-minute steps of washing with 2 x SSC; 0.1% SDS at from 55 to 65°C. The filters were evaluated by autoradiography.

20

The phage clones which were identified in this primary investigation were purified (Ausubel *et al.* (1987)). In subsequent analyses, one phage clone, i.e. P12 turned out to be potentially positive. A λ DNA preparation carried out on this phage (Ausubel *et al.* (1987)), and the subsequent restriction digestion with enzymes which release the
25 genomic insert in fragments, showed that this phage clone contains an insert of approx. 15 kb in the vector (Fig. 2).

In order to isolate the complete hTC gene sequence, in each case from 1 to 1.5×10^6 phages were screened, in independent experiments, with in each case different
30 radioactively labelled probes, as described above.

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The phage clones which were identified in these primary investigations, and which were positive for the corresponding probes, were purified. The phage clone P17 was found to contain an hTC cDNA fragment of about 250 bp in length (position 1787 to 2040 in Fig. 6). The phage clone P2 was identified as containing an hTC cDNA
5 fragment of about 740 bp in length (position 1685 to 2349 plus 2531 to 2607 in Fig. 6 [deletion 2; cf. Example 5]). The phage clones P3 and P5 were found to contain a 3' hTC cDNA fragment of 420 bp in length (position 3047 to 3470 in Fig. 6). After the λ DNA had been prepared from these phages, and subsequently subjected to restriction digestion with enzymes which release the genomic insert in fragments, the
10 inserts were subcloned into plasmids (Example 4).

Example 3

In order to investigate whether the 5' end of the hTC cDNA was also present in the
15 insert in the recombinant phage clone P12, the λ DNA from this clone was hybridized, in a Southern blot analysis, with a radiactively labelled hTC cDNA fragment of about 440 bp in length (position 1 to 440 in Fig. 6) from the extreme 5' region (Fig. 3).

20 Since the isolated λ DNA from the positive clone also hybridizes with the extreme 5' end of the hTC cDNA, this phage probably also contains the 5' sequence region flanking the ATG start codon.

Example 4

25 In order to subclone the entire 15 kb insert in the positive phage clone P12 in the form of subfragments, and subsequently to sequence these fragments, restriction endonucleases which, on the one hand, release the entire insert from EMBL3 Sp6/T7 (cf. Example 2) and, in addition, cut within the insert, were selected for digesting the
30 DNA.

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In all, two Xho I subfragments, of about 8.3 and about 6.5 kb in length, respectively, and three Sac I subfragments, of about 8.5, about 3.5 and about 3 kb in length, respectively, were subcloned into the pBluescript KS(+) vector (from Stratagene). The 5123 bp 5'-flanking nucleotide sequence of the ghTC gene region, starting from the ATG start codon, was determined by analysing the sequences of these fragments (Fig. 4; corresponding to SEQ ID NO 1). Fig. 4 depicts the first 5123 bp (starting from the ATG start codon). Fig. 10 depicts the entire cloned 5' sequence (corresponding to SEQ ID NO 3).

10 In order to subclone the entire insert, of approx. 14.6 kb in size, in phage clone P17 in the form of subfragments, restriction endonucleases which, on the one hand, release the entire insert from EMLB3 Sp6/T7 and, in addition, cut a few times within the insert, were selected for digesting the DNA. Three XhoI/BamHI fragments, of 7.1 kb, 4.2 kb and 1.5 kb in size, respectively, and one BamHI fragment, of 1.8 kb in size, were subcloned by means of using a combination digestion with the enzymes XhoI and BamHI. Combination restriction digestion with the enzymes XhoI and XbaI resulted in a XhoI/XbaI fragment of 6.5 kb in size, and two XhoI fragments, of 6.5 kb and 1.5 kb in size, respectively, being cloned.

20 Digestion with the restriction enzyme XhoI was used to subclone the insert, of approx. 17.9 kb in size, in phage clone P2 in the form of subfragments. In all, three XhoI subfragments, of 7.5 kb, 6.4 kb and 1.6 kb in length, respectively, were cloned. Four SacI fragments, of 4.8 kb, 3 kb, 2 kb and 1.8 kb in size, respectively, were additionally subcloned by digesting with the restriction enzyme SacI.

25 The insert, of approx. 13.5 kb in size, in phage clone P3 was subcloned by digesting with the restriction enzymes SacI and/or XhoI. Six SacI subfragments, of 3.2 kb, 2 kb, 0.9 kb, 0.8 kb, 0.65 kb and 0.5 kb in length, respectively, and two XhoI subfragments, of 6.5 kb and 4.3 kb in length, respectively, were obtained in this connection.

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The insert, of approx. 13.2 kb in size, in phage clone P5 was subcloned by digesting with the restriction enzymes *SacI* and/or *XhoI*. In all, *SacI* fragments of 6.5 kb, 3.3 kb, 3.2 kb, 0.8 kb and 0.3 kb in size, and *XhoI* fragmente of 7 kb and 3.2 kb in size, were subcloned.

5

In order to clone the hTC genomic sequence region located 3' of phage clone P17 and 5' of phage clone P2, 3 genomic walkings were carried out using the Clontech GenomeWalker™ kits (catalogue number K1803-1) and various combinations of primers. In a final volume of 50 µl, 10 pmol of dNTP mix were added to 1 µl of human GenomeWalker Library HDL (from Clontech), and a PCR reaction was carried out in 1xKlen Taq PCR reaction buffer and 1xAdvantage Klen Taq polymerase mix (from Clontech). 10 pmol of an internal gene-specific primer, and 10 pmol of the adaptor primer AP1 (5'-GTAATACGACTCACTATAGGGC-3'; from Clontech) were added as primers. The PCR was carried out in 3 steps as a touchdown PCR. First of all, denaturation was carried out at 94°C for 20 sec, and the primers were then annealed, and the DNA chain extended, at 72°C for 4 min, over 7 cycles. There then followed 37 cycles in which the DNA was denaturated at 94°C for 20 sec but the subsequent primer extension took place at 67°C for 4 min. In conclusion, there followed a chain extension at 67°C for 4 min. After this first PCR, the PCR product was diluted 1:50. One µl of this dilution was used in a second nested PCR together with 10 pmol of dNTP mix in 1xKlen Taq PCR reaction buffer and 1xAdvantage Klen Taq polymerase mix and also 10 pmol of a nested gene-specific primer and 10 pmol of the nested Marathon Adaptor primers AP2 (5'-ACTATAGGGCACGCGTGGT-3'; from Clontech). The PCR conditions corresponded to the parameters which were selected in the first PCR. As the sole exception, only 5 cycles rather than 7 cycles were selected in the first PCR step and only 24 cycles, instead of 37 cycles, were run in the second PCR step. The products of this nested genomic walking PCR were cloned into the TA Cloning Vector pCRII from InVitrogen.

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In the first genomic walking, the gene-specific primer C3K2-GSP1 (5'-GACGTGGCTCTTGAAGGCCTTG-3') and the nested gene-specific primer C3K2-GSP2 (5'-GCCTTCTGGACCACGGCATAACC-3') were used, together with the HDL library 4, and a PCR fragment of 1639 bp in length was obtained. In the second
 5 genomic walking, a PCR fragment of 685 bp in length was amplified from the HDL library 4 using the gene-specific primer C3F2 (5'-CGTAGTTGAGCACGCTGAACAGTG-3') and the nested gene-specific primer C3F (5'-CCTTCACCCTCGAGGTGAGACGCT-3. The third genomic walking mixture, using the gene-specific primer DEL5-GSP1 (5'-
 10 GGTGGATGTGACGGGCGCGTACG-3') and the nested gene-specific primer C5K-GSP1 (5'-GGTATGCCGTGGTCCAGAAGGC-3'), led to a 924 bp PCR fragments being cloned from the HDL library 1. In all, 2100 bp of the genomic hTC region located 3' of phage clone P17 were identified using this genomic walking method (see Fig. 7).

15 The subcloned fragments, and the genomic walking products, were sequenced in single-stranded form. The Lasergene Biocomputing Software (DNASTAR Inc. Madison, Wisconsin, USA) was used to identify overlapping regions and form contigs. In all, 2 large contigs were assembled from the sequences collected from
 20 phage clones P12, P17, P2, P3 and P5, and also the sequence data from the genomic walking. Contig 1 consists of sequence data from phage clones P12 and P17 and the sequence data from the genomic walking. Contig 2 was put together from the sequences from phage clones P2, P3 and P5. Overlapping phage clone regions are shown diagrammatically in Fig. 7. The sequence data from the 2 contigs are shown
 25 below. The ATG start codon in contig 1 is underlined. The TGA stop codon is underlined in contig 2.

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Contig1:

	ACTTGAGCCC	AAGAGTTCAA	GGCTACGGTG	AGCCATGATT	GCAACACCAC	AGGCCAGCCT	TGGTGACAGA	70
	ATGAGACCCCT	GTCTCAAAAA	AAAAAAAAAA	AATTGAAATA	ATATAAAGCA	TCTTCTCTGG	CCACAGTGGG	140
5	ACAAAACCCAG	AAATCAACAA	CAAGAGGAAT	TTTGAAGAACT	ATACAAACAC	ATGAAAATTA	AACAAATATAC	210
	TTCTGAATGA	CCAGTGAGTC	AATGAAGAAA	TTAAAAAGGA	AATTGAAAAA	TTTATTTAAG	CAAAATGATA	280
	CGGAAACATA	ACCTCTCAAA	ACCCACGGTA	TACAGCAAAA	GCAGTGCTAA	GAAGGAAGTT	TATAGCTATA	350
	AGCAGCTACA	TCAAAAAAGT	AGAAAAGCCA	GGCGCAGTGG	CTCATGCCCTG	TAATCCCAGC	ACTTTGGGAG	420
10	GCCAAAGGCGG	GCAGATCGCC	TGAGGTCAGG	AGTTTCGAGAC	CAGCCTTGACC	AACACAGAGA	AACCTTGTGG	490
	CTACTAAAAA	TACAAAAATTA	GCTGGGCATG	GTGGCACATG	CCTGTAATCC	CAGCTACTCG	GGAGGCTGAG	560
	CGAGGATAAC	CGCTTGAACC	CAGGAGGTGG	AGGTTGCGGT	GAGCGGGGAT	TGCGCCATTG	GACTCCAGCC	630
	TGGGTAACAA	GAGTGAAACC	CTGTCTCAAG	AAAAAAAAAA	AAGTAGAAAA	ACTTAAAAAT	ACAACCTAAT	700
	GATGCACCTT	AAAGAACTAG	AAAAGCAAGA	GCAAACTAAA	CCTAAAATTG	GTAAAAGAAA	AGAAATATA	770
	AAGATCAGAG	CAGAAATAAA	TGAAACTGAA	AGATAACAAT	ACAAAAGATC	AACAAAATTA	AAAGTTGGTT	840
15	TTTTGAAAAG	ATAAACAAAA	TTGACAAACC	TTTGCCGAGA	CTAAGAAAAA	AGGAAAGGAG	ACCTAAATAA	910
	ATAAAGTCAG	AGATGAAAAA	AGAGACATTA	CAACTGATAC	CACAGAAATT	CAAAGGATCA	CTAGAGGCTA	980
	CTATGAGCAA	CTGTACACTA	ATAAATTGAA	AAACCTAGAA	AAAATAGATA	AATTCTCTAG	TGCATACAC	1050
	CTACCAAGAT	TGAAGCATGA	AGAAATCCAA	AGCCCAACCA	GACCAATAAC	AATATGGGGA	TTAAAGCCAT	1120
	AATAAAGACT	CTCCTAGCAA	AGAGAAGCCC	AGGACCCAAT	GGCTTCCCTG	CTGGATTTTA	CCAATCATTT	1190
20	AAAGAAGAAT	GAATTCCAAT	CCTACTCAAA	CTATTCTGAA	AAATAGAGGA	AAGAATACIT	CCAAACTCAT	1260
	TCTACATGGC	CAGTATTACC	CTGATTCCAA	AAACAGACAA	AAACACATCA	AAAACAAACA	AACAAAAAAA	1330
	CAGAAAGRAA	GAAAACATCA	GGCCAATATC	CTGTATGAAT	ACTGATACAA	AAATCCTCAA	CAAAACATCA	1400
	GCAACCCAAA	TTAAACAACA	CCTTCGAAGG	ATCATTCAAT	GTGATCAAGT	GGGATTTATT	CCAGGGATGG	1470
25	AAGGATGGTT	CAACATATGC	AAATCAATCA	ATGTGATACA	TCATCCCAAC	AAAATGAAGT	ACAAAACTA	1540
	TATGATTATT	TCACCTTATG	CAGAAAAAGC	ATTGTATAAA	ATTCTGCACC	CTTCTATGTA	AAAACCTCTA	1610
	AAAAACCAAG	TATACAAGAA	ACATACAGGC	CAGGCACAGT	GGCTCACACC	TGCGATCCCA	GCACCTCTGG	1680
	AGGCCAAGGT	GGGATGATTG	CTTGCGGCCA	GGAGTTTGAG	ACTAGCCTGG	GCAACAAAT	GAGACCTGGT	1750
	CTACAAAAAA	CTTTTTTAAA	AAATTAGCCA	GGCATGATGG	CATATGCCTG	TAGTCCCAGC	TAGTCTGGAG	1820
30	GGTGAAGTGG	GAGAATCACT	TAAGCCTAGG	AGGTCGAGGC	TGCAGTGAGC	CATGAACATG	TCACCTGTAT	1890
	CCAGCCTAGA	CAACAGAAC	AGACCCCACT	GAATAAGAA	AAGGAGAAGG	AGAAGGGAGA	AGGAGGGAG	1960
	AAGGGAGGAG	GAGGAGAGG	AGGAGGTGGA	GGGGAAGTGG	AAGGGGAAGG	GGAAAGGAAA	GAGGAAGAG	2030
	AAGAACAATA	TTTCAACATA	ATAAAGCCCT	TATATGACAG	ACCGAGGTAG	TATTATGAGG	AAAACTGAA	2100
	AGCCTTTCTT	CTAAGATCTG	GAAATGACA	AGGGCCCACT	TTCCACCTAG	TGATTCAACA	TAGTACTAGA	2170
	AGTCTTAGCT	AGAGCAATCA	GATAAGAGAA	AGAAATAAAA	GGCATCCAAA	CTGGAAGGGA	AGAACTCAAA	2240
35	TTATCCTGTT	TGCAGATGAT	ATGATCTTAT	ATCTGGAAAA	GACTTAGAGC	ACCACTAAAA	AACATTATGA	2310
	GCTGAAATTT	GGTACAGCAG	GATACAAAAT	CAATGTACAA	AAATCAGTAG	TATTTCTATA	TTCCAACAGC	2380
	AGAAATCTG	AAAAAGAAAC	CAAAAAAGCA	GCTACAAATA	AAATTAACAA	GCTAGGAATT	AACCAAGAA	2450
	GTGAAAGATG	TCTACAATGA	AAACTATAAA	ATGTTGATAA	AAGAAATTGA	AGAGGGCACA	AAAAAGGAAA	2520
40	AGATATTCCA	TGTTCAATGA	TTGGAAGAA	AAATCTGTTT	AAATGTCCA	TACTACCCAA	AGCAATTTAC	2590
	AAATTCAATG	CAATCCCTAT	TAAATACTA	ATGACGTTCT	TCACAGAAAT	AGAAGAAACA	ATTTAAGAT	2660
	TTGTACAGAA	CCACAAAAGA	CCCAGAAATG	CCAAAGCTAT	CCTGACCAAA	AAGAACAAAA	CTGGAAGCAT	2730
	CACATTACCT	GACTTCAAT	TATACTACAA	AGCTATAGTA	ACCCAAACTA	CATGGTACTG	GCATAAAAAC	2800
	AGATAGAGCA	TGGACCAAG	GAACAGAAAT	GAGAATCCAG	AAACAAATCC	ATGCATCTAC	AGTGAATCAA	2870
45	TTTTTGACAA	AGGTGCCAAG	AACATACCTT	GGGGAAGAA	TAATCTCTTC	AATAAATGGT	GCTGGAGGAA	2940
	CTGGATATCC	ATATGCAAAA	TAACAATACT	AGAACTCTGT	CTCTCACCAT	ATACAAAAGC	AAATCAAAAT	3010
	GGATGAAAGG	CTTAAATCTA	AAACCTCAAA	CTTTGCAACT	ACTAAAAGAA	AACACCGGAG	AAACTCTCCA	3080
	GGACATTGGA	GTGGGCAAG	ACTTCTTGAG	TAATTCCTTG	CAGGCACAGG	CAACCAAGGC	AAAAACAGAC	3150
	AAATGGGATC	ATATCAAGTT	AAAAAGCTTC	TGCCAGCAAA	AGGAACAAT	CAACAAAGAG	AAGAGCAAC	3220
50	CCACAGAATG	GGAGAATATA	TTTGCAAACT	ATTCACTTAA	CAAGGAATTA	ATAACCACTA	TATATAAGGA	3290
	GCTCAAACTA	CTCTATAAGA	AAAAACCTTA	ATAAGCTGAT	TTTCAAAAA	AAGCAAAAGA	TCTGGGTAGA	3360
	CATTCTCTCA	AATAAGTCAT	ACAAATGGCA	AACAGGCATC	TGAAAATGTG	CTCAACACCA	CTGATCATCA	3430
	GAGAAATGCA	AATCAAACT	ACTATGAGAG	ATCATCTCAT	CCAGTTTAAA	ATGGCTTTTA	TTCAAAAGAC	3500
	AGGCAATAAC	AAATGCCAGT	GAGGATGTGG	ATAAAGGAA	ACCCTTGGAC	ACTGTTGGTG	GGAAATGAAA	3570
55	TTGCTACCA	TATGGAGAAC	AGTTTGAAAG	TTCTCAAAA	AACATAAAAT	AAAGCTACCA	TACAGCAATC	3640
	CCATTGCTAG	GTATATACTC	CAAAAAGGGG	AAATCAGTGA	TCAACAAGCT	ATCTCCACTC	CCACATTTAC	3710
	TGCAGCACTG	TTCATAGCAG	CCAAGGTTTG	GAAGCAACCT	CAGTGTCCAT	CAACAGACGA	ATGGAAAAAG	3780
	AAAATGTGGT	GCACATACAC	AATGGAGTAC	TACGACGCCA	TAAAAAGAA	TGAGATCTTG	TCAGTTGCAA	3850
	CAGCATGGGG	GGCACTGGTC	AGTATGTTAA	GTGAAATAAG	CCAGGCACAG	AAAGACAAC	TTTTCATGTT	3920
60	CTCCCTTACT	TGTGGGAGCA	AAAATTAATA	CAATTGACAT	AGAAATAGAG	GAGAATGGTG	GTCTTAGAGG	3990
	GGTGGGGGAC	AGGGTGACTA	GAGTCAACAA	TAATTTATTG	TATGTTTTAA	AATAACTAAA	AGAGTATAAT	4060
	TGGGTTGTTT	GTAAACACAA	GAAAGGATAA	ATGCTTGAAG	GTGACAGATA	CCCCATTTC	CCTGATGTGA	4130
	TTATTACACA	TTGTATGCCT	GTATCAAAAT	ATCTCATGTA	TGCTATAGAT	ATAAACCTTA	CTATATTAAA	4200
	AATTAAAAAT	TTAATGGCCA	GGCAGGTTGG	CTCATCTCCG	TAATCCCAAG	ACTTTGGGAG	GGCAGGGGGG	4270
65	GTGGATCACC	TGAGGTCAGG	AGTTTGAAC	CAGTCTGGCC	ACCATGATGA	AACCTGTCT	CTACTAAAGA	4340
	TACAAAAAAT	AGCCAGGCGT	GGTGGCAGAT	ACCTGTAGTC	CCAATCTACT	AGGAGGCTGA	SACAGGAGAA	4410
	TTGCTTGAAC	CTGGGAGGCG	GAGGTTGGAG	TGAGCCGAGA	TCATGCCACT	GCACCTGACG	CTGGGTGACA	4480
	GAGCAAGACT	CCATCTCAAA	ACAAAAACAA	AAAAAGAAG	ATTAAAAATG	TAATTTTTAT	GTACCGTATA	4550
	AATATATACT	CTACTATATT	AGAAGTTAAA	AATTAAAAAC	ATTATAAAG	GTAAATTAAC	ACTTAATCTA	4620
70	AAATAAGAAC	AATGTATGTG	GGGTTTCTAG	CTTCTGAAGA	AGTAAAGATT	ATGGCCACGA	TGGCAGAAAT	4690
	GTGAGGAGGG	AACAGTGGAA	GTTACTGTGT	TTAGACGCTC	ATACTCTCTG	TAAGTGACTT	AATTTTAACC	4760
	AAAGACAGGC	TGGGAGAAAT	TAAAGAGGCA	TTCTATAAGC	CCTAAAAACA	CTGCTAATAA	TGGTGAAAGG	4830
	TAATCTCTAT	TAATTACCAA	TAATTACAGA	TATCTCTAAA	ATCGAGCTGC	AGAAATGGCA	CTCTGTATCA	4900
	CACCGTCCCT	TCATTACCGG	TGCTTTTTTT	CTTGTGTGCT	TGGAGATTTT	CGATTGTGTG	TTCTGTGTTG	4970
75	GTTAAACTTA	ATCTGTATGA	ATCCTGAAAC	GAAAAATGGT	GGTGATTTC	TCCAGAAGAA	TAGAGTACC	5040
	TGGCAGGAAG	CAGGTGGCTC	TGTGGACCTG	AGCCACTTCA	ATCTTCAAGG	GTCTCTGGCC	AAGACCCAGG	5110

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	TGCAAGGCAG	AGGCCTGATG	ACCGGAGGAC	AGGAAAGCTC	GGATGGGAAG	GGCGATGAG	AAGCCTGCCT	5180
	CGTTGGTGAG	CAGCGCATGA	AGTGCCCTTA	TTTACGCTTT	GCAAGATTG	CTCTGGATAC	CATCTGGAAA	5250
	AGGCGGCCAG	CGGGAATGCA	AGGAGTCAGA	AGCCTCCTGC	TCAAAACCAG	GCCAGCAGCT	ATGGCGCCCA	5320
5	CCCGGGCGTG	TGCCAGAGGG	AGAGGAGTCA	AGGCACCTCG	AAGTATGGCT	TAAATCTTTT	TTTCACCTGA	5390
	AGCAGTGACC	AAGGTGTATT	CTGAGGGAAG	CTTGAGTTAG	GTGCCTTCTT	TAAAACAGAA	AGTCATGGAA	5460
	GCACCTCTCT	CAAGGGAAAA	CCAGACGCCC	GCTCTGCGGT	CATTTACCTC	TTTCTCTCT	CCCTCTCTTG	5530
	CCCTCGCGGT	TTCTGATCGG	GACAGAGTGA	CCCGCTGGGA	GCTTCTCCGA	GCCCGTGCTG	AGGACCTCTC	5600
	TGCAAGGGGC	TCCACAGACC	CCCGCCCTGG	AGAGAGSAGT	CTGAGCCTGG	CTTAATAACA	AACTGGGATG	5670
10	TGGCTGGGGG	CGGACAGCGA	CGGCGGGATT	CAAAGACTTA	ATTCCATGAG	TAAATTCAC	CTTTCCACAT	5740
	CCGAATGGAT	TTGGATTTTA	TCTTAATATT	TTCTTAAATT	TCATCAATA	ACATTACAGG	CTGCAGAAAT	5810
	CCAAAGGCGT	AAAACAGGAA	CTGAGCTATG	TTTGCCAAAG	TCCNAGGACT	TAATAACCAT	GTTCAGAGGG	5880
	ATTTTTCGCC	CTAAGTACTT	TTTATTGGTT	TTCATAAAGT	GGCTTAGGGT	GCAAGGGAAA	GTACACGAGG	5950
15	AGAGGCGCTG	GCGGCAGGGC	TATGAGCAGC	GCAGGGCCAC	CGGGGAGAGA	GTCCCGGGCC	TGGGAGGCTG	6020
	ACAGCAGGAC	CACTGACCGT	CCTCCCTGGG	AGCTGCCACA	TTGGGCAACG	GGAAGGCGCG	CACGCTCGGT	6090
	GTGACTCAGG	ACCCCATACC	GGCTTCTCTG	GCCACCCAC	ACTAACCCAG	GAAGTCACGG	AGCTCTGAAC	6160
	CCGTGGAAAC	GAACATGACC	CTTGCCCTGCC	TGCTTCCCTG	GGTGGGTCAA	GGGTAAATGAA	GTGGTGTGCA	6230
	GGAAATGGCC	ATGTAAATTA	CACGACTCTG	CTGATGGGGA	CCGTTCCTTC	CATCATTATT	CATCTTCACC	6300
	CCCAAGGCTT	GAATGATTCC	AGCAACTTCT	TCGGGTGTGA	CAAGCCATGA	CAAAACTCAG	TACAACACCC	6370
20	ACTCTTTTAC	TAGGCCACAC	GAGCAGGSCC	CACACCCCTG	ATATATTAA	AGTCCAGGAG	AGATGAGGCT	6440
	GCTTTTCAGC	ACCGGCTGG	GGTGACAACA	GCGGCTGAAC	AGTCTGTTCC	TCTAGACTAG	TAGACCCCTG	6510
	CAGGCACCTC	CCCAGATTCT	AGGGCCTGGT	TGCTGCTTCC	CGAGGGCGCC	ATCTGCCCTG	GAGACTCAGC	6580
	CTGGGGTGCC	ACACTGAGGC	CAGCCCTGTC	TCCACACCTC	CCGCTCCAG	GCCTCAGCTT	CTCCAGCAGC	6650
	TTCTTAAAC	CTGGGTGGGC	CGTGTCTCAG	CGCTACTGTC	TCACCTGTCC	CACCTGTGTC	TGTCTCAGCG	6720
25	ACGTAGCTCG	CACGGTTCCT	CCTCACATGG	GGTGTCTGTC	TCCTTCCCCA	ACACTCACAT	CGCTTGAAGG	6790
	GAGGAGATTG	TGGCGCTCCC	AGACTGCGTC	CTCTGAGCCT	GAACCTGGGT	CGTGGCCCCC	GATGCAGGTT	6860
	CCTGGCGTCC	GGCTGCACGC	TGACCTCCAT	TTCCAGGCGC	TCCCGTCTC	CTGTCACTCG	CCGGGGCCTG	6930
	CCGSGTGTTT	CTTCTGTTTC	TGTGCTCCTT	TCCACGTCCA	GCTGCGTGTG	TCTCTGCCCG	CTAGGGTCTC	7000
	GGGGTTTTTA	TAGGCATAGG	ACGGGGCGGT	GGTGGGCCAG	GGCGCTCTTG	GGAAATGCAA	CATTTGGGTG	7070
30	TGAAAGTAGG	AGTGCCTGTC	CTCACCTAGG	TCCACGGGCA	CAGGCCCTGG	GATGGAGCCC	CCGCCAGGGA	7140
	CCCGCCCTTC	TCTGCCACGC	ACTTTCCTGC	CCCCCTCCCT	CTGGAAACAC	GAGTGGCAGT	TCCACAAGC	7210
	ACTAAGCATC	CTCTTCCCAA	AAGACCCAGC	ATTGGCACCC	CTGGACATT	GCCCCACAGC	CCTGGGAATT	7280
	CACGTGACTA	CGCACATCAT	GTACACACTC	CCGTCCACGA	CCGACCCCGC	CTGTTTTATT	TTAATAGCTA	7350
	CAAAACAGGG	AAATCCCTGC	TAAATGTGCC	TTTAACAAAC	TGGTTAAACA	AACGGGTCCA	TCCGCACGGT	7420
35	GGACAGTTCC	TCACAGTGAA	GAGGAACATG	CCGTTTATAA	AGCCTGCAGG	CATCTCAAGG	GAATTACGCT	7490
	GAGTCAAAAC	TGCCACCTCC	ATGGGATACG	TACGCAACAT	GCTCAAAAG	AAAGAATTTC	ACCCCATGSC	7560
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	AAGCCAGTTT	CCTGTTCTCG	ATGGTATTGG	CTCAGTTATG	GGAGACTAAC	CATAGGSGAG	TGGGATGGG	7700
	GGAAACCCGA	GGCTGTGCCA	TCTTTGCCAT	GCCCGAGTGT	CCTGGGCAGG	ATAATGCTCT	AGAGATGCCC	7770
40	ACGTCTGAT	TCCCCCAAAC	CTGTGGACAG	AACCGGCCCG	GCCCCAGGGC	CTTTGCAGGT	GTGATCTCGG	7840
	TGAGGACCTT	GAGGTCTGGG	ATCCTTCGGG	ACTACCTGCA	GGCCCCAAAA	GTAAATCCAG	GGTCTGGGA	7910
	AGAGGCGGCG	AGGAGGGTCA	GAGGGGGGCA	GCCTCAGGAC	GATGGAGGCA	GTCACTCTGA	GGCTGAAAG	7980
	GGAGGGAGGG	CCTCGAGGCC	AGGCCCTGCA	GGCCTCCAG	AAGCTGGAAA	AAGCGGGGAA	GGGACCCCTC	8050
	ACGGAGCCTG	CAGCAGGAAG	GCACGGCTGG	CCCTTAGCCC	ACCAGGGCCC	ATCGTGGACC	TCCGGCTCC	8120
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	CTGAGACAGA	GTTATGCTCT	TGTTGCCAG	GCTGGAGTGC	AGCGGCATGA	TCTTGGCTCA	CTGCAACCTC	8400
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50	ACACCCGGCT	AATTTTGTAT	TTTTAGTAGA	GATGGGCTTT	CACCATGTTG	GTCAAGCTGA	TCTCAAAATC	8540
	CTGACCTCAG	GTGATCCGCG	CACCTCAGCC	TCCCAAGATG	CTGGGATTAC	AGGCATGAGC	CACCTACAGC	8610
	GGCCTATTTA	ACCATTTTAA	AACTTCCCTG	GGCTCAAGTC	ACACCCACTG	GTAAAGGAGT	CATGGAGTTC	8680
	AATTTCCCTC	TTACTCAGGA	GTTACCTCC	TTTGATATTT	TCTGTAATTC	TTCGTAGACT	GGGATACAC	8750
	CGTCTCTTGA	CATATTTCAC	GTTTCTGTGA	CCACCTGTTA	TCCCATGGGA	CCCAGTGCAG	GGGCAAGCTG	8820
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	AAGTGTGGAC	ACTGTCTGTA	ATCTCAATGT	CTCAGTGTGT	GCTGAAACAT	GTAGAAATTA	AAGTCCATCC	8960
	CTCCTACTCT	ACTGGGATTG	AGCCCCCTCC	CTATCCCCCC	CCAGGGGCG	AGGAGTTCCT	CTCACTCCTG	9030
	TGGAGGAAGG	AATGATACTT	TGTTATTTTT	CACGTGCTGT	ACTGAATCCA	CTGTTTCATT	TGTTGGTTTG	9100
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60	GCTTACTGCA	GCCTCTGCCT	CCCAGGTTCA	AGTGATTCTC	CTGCTTCCCG	CTCCCATTTG	GCTGGGATTA	9240
	CAGGCACCCG	CCACCATGCC	CAGCTAATTT	TTTGTATTTT	TAGTAGAGAC	GGGGGTGGGT	GGGGTTTACC	9310
	ATGTTGGCCA	GGCTGGTCTC	GAACCTTCTGA	CCGAGATGA	TCCACCTGCC	TCTGCCTCCT	AAAGTGCTGG	9380
	GATTACAGGT	GTGAGCCACC	ATGCCCAGCT	CAGAAATTAC	TCTGTTTAGA	AACATCTGGG	TCTGAGGTAG	9450
	GAAGCTCACC	CCACTCAACT	GTTGTGGTGT	TTTAAAGCAA	TGATAGAATT	TTTTTATTGT	TGTTAGAACA	9520
65	CTCTTGATGT	TTTACACTGT	GATGACTAAG	ACATCATCAG	CTTTTCAAAG	ACACACTAAC	TGCACCCATA	9590
	ATACTGGGGT	GTCTTCTGGG	TATCAGCAAT	CTTCATTGAA	TGCGGGGAGG	CGTTTCTCTG	CCATGCACAT	9660
	GGTGTTAATT	ACTCCAGCAT	AATCTTCTGC	TTCCATTTCT	TCTCTTCCCT	CTTTTAAAT	TGTGTTTTCT	9730
	ATGTTGGCTT	CTCTGCAGAG	AACCACTGTA	AGCTACAACT	TAACTTTTGT	TGGAAACAA	TTTCCAAACG	9800
	GGCCCTTTTG	CCTAGTGCCA	GAGACAATTC	ACAAACACAG	CCCTTTAAAA	AGGCTTAGGG	ATCACTAAGG	9870
70	GGATTCTTAG	AAGAGCGACC	TGTAATCTTA	AGTATTACCA	AGACGAGGCT	AACCTCCAGC	GAGCGTGACA	9940
	GGCCAGGGAG	GGTGGGACGC	CTGTTCAAA	GCTAGCTCCA	TAAATAAAGC	AATTTCTCTC	GGCAGTTTCT	10010
	GAAAGTAGGA	AAGGTTACAT	TAAAGCTTGC	GTTTGTGAGC	ATTTCACTGT	TTGCCAGCT	CAGTTACAGC	10080
	ATCCCTGCAA	GGCCTCGGGA	GACCCAGAA	TTTCTGCGCC	CCTTAGATCC	AAACTTGAGC	AACCCGGAGT	10150
	CTGGATTCTT	GGGAAGTCTT	CAGCTGTCTT	GCGTGTGTGC	CGGGGCCCCA	GGTCTGGAGG	GGACCACTGG	10220
75	CCGCTGTGGT	TCTACTGCTG	GGCTGGAAT	GCGGCTCTCT	AGCTCTGCAG	TCCGAGGCTT	GAGCCAGGCT	10290
	GGCTGGACCC	CGAGGCTGCC	CTCCACCTCT	TGCGGGCGGG	ATGTGACCAG	ATGTTGCCCT	CATCTGCCAG	10360
	ACAGAGTGGC	GGGGGCCAGG	GTCAGGGCCG	TTGTGGCTGG	TGTGAGGGCG	CGGGTGGCGG	GCCAGCAGGA	10430
	CGGCTGTGGT	CAATTTCCCA	CCCTTTCTCG	ACGSGACCCG	CCCGCTGGGT	GATTAACAGA	TTTGGGGTGG	10500
	TTTGCTCATG	GTGGGGACCC	CTCGTCTGCT	GAGAACCTGC	AAAGAGAAAT	GACGGGCTCG	TGTCAAGSAG	10570

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	CCCCAAGTCG	GGGGAAGTGT	TGCAGGGAGG	CACCTCCGGG	GGTCCCGCGT	GCCCGTCCAG	GGAGCAATGC	10640
	GTCCCTCGGGT	TCGTCCCGAG	CCGCGTCTAC	CGCGCTCCGT	CCTCCCGCTT	ACGTCCGGCA	TTCTGGTTCG	10710
	CCGGAGCCCG	ACGCCCCCGG	TCCGGACCTG	GAGGCAGCCC	TGGGTCTCCG	GATCAGGCCA	GGGGCCAAAG	10780
5	GGTCCGCGCA	CGCACTGT	CCCAGGGCCT	CCACATCATG	GCCCCCTCC	CGGTTACCC	CACAGCCTAG	10850
	CGCGATTGGA	CCTCTCTCCG	CTGGGCCCC	CGCTGGCGTC	CCTGCACCC	GGGAGCGCGA	CGGGCGCGCG	10920
	GGCGGGGAG	CGCGGGCCAG	ACCCCGGGGT	CCGCGCGGAG	CAGCTGCGCT	GTCCGGGCGA	GGCCGGGCTC	10990
	CCAGTGGATT	CGCGGGGACA	GAGGCCAGG	ACCGCGCTCC	CCACGTGGCG	GAGGGACTGG	GGACCCGGGG	11060
	ACCCGTCCTG	CCCCCTTACC	TTCCAGCTCC	GCCTCCTCCG	CGCGGACCCC	GCCCCGTCCC	GACCCCTCCC	11130
	GGGTCCCGGG	CCCAGCCCCC	TCCGGGCCCC	CGCAGGCCCT	CCGCTTCCTT	TCCGCGGCCC	CGCCCTCTCC	11200
10	TCGCGGCGCG	AGTTTCAGGC	AGCGCTGCGT	CCTGTGCGC	ACGTGGGAAG	CCCTGGCCCC	GGCCACCCCC	11270
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	CGCTGGCCAC	GTTCGTGCGG	CGCCTGGGGC	CCCAGGGCTG	CGGGCTGGTG	CAGCGCGGGG	ACCCGGGCGG	11410
	TTTCCGCGCG	CTGGTGGCCC	AGTGCTGGT	GTGCGTGCCC	TGGGACGCAC	GGCCGCCCCC	CGCCGCCCCC	11480
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	GCCCGAGTGC	TGCAGAGGCT	GTGCGAGCGC	GGCGCGAAGA	ACGTGCTGGC	CTTCGCTTTC	GGCTGCTGG	11690
	ACCGGGCCCCG	CGGGGGCCCC	CCCAGGGCCT	TCACCCACAG	CGTGCGCAGC	TACCTGCCCA	ACACGGTGAC	11760
	CGAGCTCAGT	CGGGGGAGCG	GGGCTGGGGG	GCTGCTGCTG	CGCGCGGTGG	GCAGCAGCTG	GCTGGTTTCA	11830
	CTGCTGGCAC	GCTGCGCGCT	CTTTGTGCTG	GTGCTCCCA	GCTGCGCTTA	CCAGGTGTGC	GGGCGCGCGC	11900
20	TGTACCACT	CGGGCTGCGC	ACTCAGGCCC	GGCCCCCGCC	ACACGCTAGT	GGACCCCGAA	GGCTGCTGGG	11970
	ATGCGAACCG	GCCTGGAAAC	ATAGCGTCAG	GGAGGCGCGG	GTCCCGCTGG	GCCTGCCAGC	CCCGGGTSCG	12040
	AGGAGGCGCG	GGGGCAGTGC	CAGCCGAAGT	CTGCCGTTGC	CCAGAGGCCC	CAGGCGTGGC	GCTGCCCTTG	12110
	AGCCGCGAGCG	GACGCCCGTT	GGGCGAGGGT	CCTGGGCCCC	CCCGGGCAGG	ACGCGTGGAC	CGAGTCAACG	12180
	TGGTTTCTGT	GTGGTGTGAC	CTGCCAGACC	CGCCGAAGAA	GCCACCTCTT	TGGAGGGTGC	GCTCTCTGCG	12250
25	ACCGGCGACT	CCGACCCACT	CGTGGGCGCG	CAGCACCACG	CAGGCCCCCC	ATCCACATCG	CGGCCACCAC	12320
	GTCCCTGGGA	CACGCCCTGT	CCCCCGGTGT	ACGCCGAGAC	CAAGCACTTC	CTCTACTCCT	CAGGCGACAA	12390
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	GAGACCATCT	TTCTGGGTTC	CAGGCCCTGG	ATGCCAGGGA	CTCCCGCAG	GTTCGCCCGC	GTGCCCGAGC	12530
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	CCTCAAGACG	CACCTGCCCG	TGCGAGCTGC	GGTCACCCCA	GCAGCGGGTG	TCTGTGCCCG	GGAGAGAGCC	12670
	CAGGGCTCTG	TGGCGGCCCC	CGAGGAGGAG	GACACAGACC	CCCGTGCGCT	GGTGACAGTG	CTCCGCGCAG	12740
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	GGGCTCCAGG	CACACCGAAC	GCCGCTTCTT	CAGGAACACC	AAGAAGTTCA	TCTCCCTGGG	GAAGCATGCC	12880
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35	GTGAGGAGGT	GGTGGCGGTC	GAGGGCCCCG	GCCCCAGAGC	TGAATGCAGT	AGGGGCTCAG	AAAAGGGGGC	13020
	AGGCAGAGCC	CTGGTCCCTC	TGCTTCCATC	CTCAGTGGG	CACACGTGGC	TTTTCGCTCA	GGACGTCGAG	13090
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	ACTGTCTCTC	AGCACAGATC	CTGGTCCCAT	CTTTAGGTAT	GAAGAGGGCC	ACATGGGAGC	AGAGGACAGC	13860
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55	ACCCAGTTTT	GCTTTTTTGT	CTCCAGCTTC	CTTCTGTGAG	GAGAGTTTGA	GTTCTCTGAT	CAGGACTCTG	14420
	CCTGTCAATT	CTGTCTCTG	ACTTCAGATG	AGGTCACAAT	CTGCCCTTGG	CTTATGCAAG	GAGTGAGGCG	14490
	TGGTCCCCGG	GTGTCCCTGT	CACGTGCAAG	GTGAGTGAGG	CGTTGCCCCC	AGGTGTCCCT	GTACGCTGTA	14560
	GGGTGAGTGA	GGCGCGGGCC	CGGGGTGTCC	CTGTCCCCGT	CAGCGTGATT	GAGGTGTGGC	CCCCGGGTGT	14630
60	CCCTGTCAAG	TGTAGGGTGA	GTGAGGCGCC	ATCCCCGGGT	GTCCCTGTCA	CGTGTAGGGT	GAGTGAGGCG	14700
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	CCCTGTCAAG	TGTAGGGTGA	GTGAGGCGCC	GTCCCTGGGT	GTCCCTCCCC	GGTATAGGGT	GAGTGAGGCG	14910
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65	GGGTGAGTGA	GGCGCTGTCC	CTGGGTGTCC	CTGTCTCTGT	TAGGGTGAGT	GAGGCTCTGT	CCCCAGGTGT	15050
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	GGCACTGCAG	CCACAGCTTC	AGGTCCGCTT	GCCTCTGTTC	GGCTTGGCTT	GCTCAGCAGG	TGCCCGCCAC	15330
	ATGCATCTGC	CCAATACTCC	TCTCCAGCTT	TGCTCATGCG	CGAGGCTGGA	CTCTGGGCTG	CTGTGTCTGT	15400
70	CTGCGCAGTG	TTGGTGGAGA	CATCCAGAGG	AGGGTTCTCT	GTGCCCTGAA	GGAAAGCAAG	TACCCCGAGC	15470
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	TCACCTTATT	CTGGGCACTT	GGCCTCATTT	GCTTAGGCTG	GGCTCTGCTT	CCAGTCCGCC	CTTCACATGG	15610
	ATTGACGTCC	AGCCACAGGT	TGGAGTGTCT	CTGTCTGTCT	CCTGCTCTGA	GACCCACGTC	GAGGGCGGCT	15680
	GTCTCCGCGA	GGCTTCTGTA	GACTTCCCTT	TTGGGTCTTA	GTTTTGAATT	TCACTGATTT	GCTCTGAGG	15750
75	TTTCTATCTC	TCCATTGAT	GCTTTTTCTT	GGTTTATCTT	TTTCTCTCTT	TTCTAGCTTC	TGAGTTTATG	15820
	CATGGCTTTC	CCTCTAAGTG	CTGCCCTTAC	TGCACCCCTG	GTTTTGATGT	GAAGTAATCT	CAACATCAGC	15890
	CACCTTCAAG	TGTTCTTAAA	ATACCTTAAA	GTTTAAATAC	TTCTTTTAAAG	TATTTCTATT	CTGTGATTTT	15960
	TTTCTTTTGT	CAGGCTTGTG	TTTACGCTGA	AATCATTTTG	ATATCAGTGA	CTTTTAAAGT	TTCTTTAGCT	16030

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	TATTCTGTGA	TTTCTTTGAG	CAGTGAGTTA	TTTGAACACT	GTTTATGTTC	AAGATATGTA	GAGTATCAAG	16100
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	ACCAATATT	TGAAGTTTGC	GGAGCCTTGC	TTTGTGATCT	AGTGTGTGCA	TGGTTTCCAG	AACCTGTCCAT	16240
	TGTAATTTTG	ACATCCTGTC	AATAGTGGGC	ATGCATGTTT	ACTATATGCA	GCTTATTAAG	GTCCAGTGCA	16310
5	AAGCTTCTGT	CTCCTTCTAG	ATGCATGAAA	TTCCAAGAAG	GAGGCCATAG	TCCCTCACCT	GGGGATGGG	16380
	TCTGTTTATT	TCTTCTCGTT	TGGTAGCATT	TATGTGAGGC	ATTGTTAGGT	GCATGCACGT	GGTAGAATTT	16450
	TTATCTTCTT	GATGAGTGAA	TCTTTTGGAG	ACTTCTATGT	CTCTAGTAAT	CTAGTAATTC	TTTTTTTAAA	16520
	TTGCTCTTAG	TACTGCCACA	CTGGGCTTCT	TTGATTAGT	ATTTTCTGTC	TGTGTCTGTT	TTCTGCCTTT	16590
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10	AGTGGTGTGA	TCACAGGTCA	GTGTAACCTT	TACCTTCTGG	CCTGAGCCGT	CCTCTCACCT	CAGCCTCTCT	16730
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	TGCTGTGTGG	CCCAGGCTGG	TCTCAAACCT	TGGGACTCAA	GGGATCCATC	TACCTCGGCT	TCCCAAAGTG	16870
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	TGTCCTGTGA	ACAGCATGTA	GGTGAATTTT	CAATCCAGTC	TGACAGTCTG	TGTTAACTG	GATAACCTGA	17010
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	CCTGCTTCCC	TTGTTTCTCA	CCACCTCTTG	GGTTGCCATG	TGCGTTTCTT	GCCGAGTGTG	TGTTGATCCT	17150
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20	ATCTCGGCTC	ACTGCAACCT	CTGCTCTCTC	GGTTCAGACA	GTTCCTATTC	CTCAACCTCA	TGAGTAGCTG	17360
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	TGGCCAGGCT	GGTCTCAAAC	TGCTGACCTC	AAGTATCTG	CCCGCCTTGG	CCTCCACAG	TGCTGGGATT	17500
	ACAGGTGCAA	CCCACCGTGC	CCGGCATACC	TTGATCTTTT	AAAATGAAGT	CTGAAACATT	GCTACCCCTG	17570
	TCCTGAGCAA	TAAGACCCCT	AGTGTATTTT	AGCTCTGGCC	ACCCCCAGC	CTGTGTGCTG	TTTTCCCTGC	17640
	TGACTTAGTT	CTATCTCAGG	CATCTTGACA	CCCCACAAAG	CTAAGCATT	TTAATATTGT	TTTCCGTGTT	17710
25	GAGTGTTCCT	GTAGCTTTGC	CCCCGCCCTG	CTTTTCTCTC	TTTGTCTCCC	GTCTGTCTTC	TGCTCTCAGG	17780
	CCGCCCTCTG	GGGTCTCCCT	CTTTGTCTCT	TGCGTGGTTC	TTCTGTCTTG	TTATTGCTGG	TAAACCCAG	17850
	CTTTACCTGT	GCTGGCTCTC	ATGGCATCTA	CGGACGTCCG	GGGACCTCTG	CTTATGATGC	ACAGATGAAG	17920
	ATGTGGAGAC	TCACGAGGAG	GGCGGTCTAT	TGGGCCGTGT	AGTGTCTGGA	GCACACCTG	GCCAGCGTTC	17990
	CTTAGCCAGT	GAGTGACAGC	AACGTCCGCT	CGGCCCTGGT	TCAGCCTGGA	AAACCCAGG	CATGTCCGGG	18060
30	TCTGGTGGCT	CCGCCGTGTC	GAGTTTGAAG	TGCGCCAAAC	CTGCGGTGTG	GGCCAGCTC	TGACGGTGCT	18130
	GCTTGGCGGG	GGAGTGTCTG	CTTCTCTCCT	TCTGCTTGGG	AACCAGGACA	AAGGATGAGG	CTCCGAGCCG	18200
	TTGTCCGCCA	ACAGGAGCAT	AGCGTGAGCC	ATGTGGATAA	TTTTAAATTT	TCTAGGCTGG	GGCGGTGGG	18270
	TCACGCTCTG	AATCCAGCA	CTTTGGGAGG	CCAAGGCGGG	TGGATCAGCA	GGTCAGGAGG	TCGAGACCAT	18340
	CCTGGCCAA	ATGATGAAC	CCCATCTGTA	CTAATAACAC	AAAAATTAGC	TGGCGTGGT	GGCGGTGGG	18410
35	TGTAATCCCA	GCTACTCGGG	AGGCTGAGGC	AGGAGAATTG	CTTGAACCTG	GGAGTTGGAA	GTTCAGTGTA	18480
	GCCGACATTG	CACCACTGCA	CTCCAGCCTG	GCAACACAGC	GAGACTCTGT	CTCAAAAAAA	AAAAAAAATA	18550
	AAAAAAAATA	AATTTAGTA	GGCAATTA	AAAAAGTAAA	AAGAAAAGGT	GAAATTAATG	TAATAATAGA	18620
	TTTTACTGAA	CCCCAGCATG	TCCACACCTC	ATCATTTTAT	GGTGTATTG	GTGGGAGCAT	CATCTACAGG	18690
	ACATTTGACA	TTTTTTGAGC	TTTGTCTGGG	GGATCCCGTG	TGTAGGTCCC	GTGCGTGGCC	ATCTCGGCTC	18760
40	GGACCTGCTG	GGCTTCCCAT	GGCCATGGCT	GTGTACACAG	ATGGTGCAGG	TCCGGGATGA	GGTCCGAGG	18830
	CCCTCAGTGT	GCTGGATGTG	CAGTGTCCCG	ATGGTGCACG	TCTGGGATGA	GGTCCGAGG	CCCTGCTGTT	18900
	AGCTGGATGT	GTGGTGTCTG	GATGGTGCAG	GTACGGGGTG	AGGTCTCCAG	GGCCTCGGTG	GGCTGAGTGT	18970
	ATGGAGTCCG	GATGATGCAG	GTCCGGGGTG	AGGTCCCGAG	GGCCTGCTGT	GAGCTGGATG	TGTGGTGTCT	19040
	GGATGGTGCA	GGTCAGGGGT	GAGGTCTCCA	GGCCCTCGGT	AAGCTGGAGG	TATGGAGTCC	GGATGATGCA	19110
45	GGTCCGGGGT	GAGGTGCGCA	GGCCCTGCTG	TGAGCTGGAT	GTGTGGTGTG	TGGATGGTGC	AGGTCTGGGG	19180
	TGAGGTCAAC	AGGCCCTGCG	GTGAGCTGGG	TGTGGGGTGT	CTGGATGGTG	CAGGTCTGGA	GTGAGGTCCG	19250
	CAGACGGTGC	CAGACCATGC	GGTGAGCTGG	ATATCGGGTG	TCCGGATGGT	GCAGGTCTGG	GGTGAGGTTG	19320
	CCAGGCCCTG	CTGTGAGTTG	GATGTGGGGT	CTCCGATGTC	TGCGGATCCG	GTGTGAGGTC	ACCAGGCCCT	19390
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	GCAGTGTCCA	GATGGTGCAG	GTCCGGGGTG	AGGTCCGCCAG	ACCTTCCGGT	GAGCTGGATG	TGCGGTGTCT	19600
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	GGTCCGGGGT	GAGGTGCGCA	GACCTGTCTG	TGAGCTGGAT	GTCCGGTGTG	TGGATGGTAC	GGCTCTGGAG	19740
	TGAGGTGCGC	AGACCTGTCT	GTGAGCTGGA	TATCCGGTGT	CCGGATGGTG	CAGGTGAGGG	GTGAGGTCTC	19810
55	CAGGCCCTCG	GTGAGCTGGA	GGTATGGAGT	CCGGATGATG	CAGGTCCGGG	GTGAGGTCCG	CAGGCCCTGC	19880
	TGTGAACCTG	ATGTGCGGGC	TCTGGATGGT	GCAGGTCTGG	GGTGTGGTGG	CCAGGCCCTC	GGTGAGCTGG	19950
	AGGTATGGAG	TCCGGATGAT	GCAGGTCCGG	GGTGAGGTGG	CCAGGCCCTG	CTGTGAGCTG	GATGTGCGGC	20020
	GTCTGGATGG	TGCAGGTCTG	GGGTGTGGTC	GCCAGGCCCT	CGGTGAGCTG	GAGGTATGCA	GTCCGGATGA	20090
	TGCAGGTCCG	GGGTGAGGTT	GCCAGGCCCT	GCTGTGAGCT	GGATGTGCTG	TATCCGGATG	GTGAGTCCG	20160
60	GGGTGAGGTC	GCCAGGCCCT	GCTGTGAGCT	GGATGTGCTG	TATCCGGATG	CTGCAGGTCT	GGGGTGAAGT	20230
	CACCAAGGCC	TGCGGTGAGC	TGGTTGTGCG	GTGTCCGGTT	GCTGCAGGTC	CGGGGTGAGT	TGCGCAGGCC	20300
	CTCGGTGAGC	TGATGTGCTG	GTGTCCCGGT	GTCCGGATGG	TGCAGGTCCA	GGGTGAGGTC	GCTAGGCCCT	20370
	TGGTGGGCTG	GATGTGCGGT	GTCCGGATGG	TGCAGGTCTG	GGGTGAGGTC	GCCAGGCCCT	TGCTGAGCTG	20440
65	GATGTGCGGT	GTCTGCATGG	TGCAGGTCTG	GGGTGAGGTC	GCCAGGCCCT	TGCTGAGGTC	GATGTGTGGT	20510
	GTCCGGATGG	TGCAGGTCTG	GGGTGAGGTC	GCCAGGCCCT	GCTGTGAGCT	GGATGTGCGG	TGCTGTGATG	20580
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	CGGGGTGAGG	TGCGCAGGCC	CTCCGGTTAG	CTGCATATGC	GGTGTCCGGA	TGGTGCAGGT	CGGGGTGAG	20720
	GTCAACAGGC	CCTGCGGTTA	GCTGGATGTG	CGGTGTCTGG	ATGGTGCAGG	TCCGGGGTGA	GGTGCAGG	20790
70	CCCTGCTGTG	AGCTGGATCT	GCTGTATCCG	GATGGTSCAG	GTCCGGGGTG	AGGTGCGCAG	GCCCTGCAST	20860
	GAGCTGGATG	TGCTGTATCC	GGATGGTSCA	GCTGTGCGGT	GAGGTGCGCA	GGCCTGCGGG	TGAGCTGGAT	20930
	ATGCGGTGTC	GGATGCTGCA	GGTCCGGGGT	GAGGTGACCA	GGCCTGCGGG	TGAGCTGGAT	GTGCGGTGTC	21000
	CGGATGCTGC	AGGTCTGGGG	TGAGGTGCGC	AGGCCCTGCT	GTGAGCTGGA	TGTGCTGTAT	TCGGATGGGT	21070
	CAGGTGCGGG	GTGAGGTGCG	CAGGCCCTGC	GGTGAGGTGG	ATGTGCTGTA	TCCGGATGGT	GCAGGTCTGG	21140
75	CSTGAGGTCC	CCAGGCCCTG	CAGGTGAGCTG	GATGTGCACT	GTACGGATGG	TGCAGGTGCG	GGGTGAGGTC	21210
	GCCAGGCCCT	CGGGTGGGCT	GTATGTGTGT	TGTGTGSAAT	GTGAGGTGCT	CGGGTGAAGT	CGGGTGAAGT	21280
	TGCGGTGAGC	TGGATGTGCT	GTGTCTGGAT	GCTGTGAGGT	CGGGGTGAGT	TGCGCAGGCC	CTCCGTGAGC	21350
	TGGATGTGCT	GTGTCCCGGT	TGCCGAATGG	TGCCAGGTGCA	GGGTGAGGTC	TGCGCAGGCC	TGCTGGGTGCT	21420
	GATGTGCGGT	GTCCGATGAG	TGCCAGGTGCT	GGGTGAGGTC	GCCAGGCCCT	TGCTGAGGTC	GATGTGCGGT	21490

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5	GTCCGGATGG	TGCAGGTCGG	GGGTGAGGTC	ACCAGGCCCT	CGGTGATCTG	GATGTGGCAT	GTCTTCTCG	21560
	TTTAAGGGGT	TGGCTGTGTT	CGGGCCGGCAG	AGCACCGTCT	CGGTGAGGAG	ATCCTGGCCA	AGTTCTCTGA	21630
	CTGGCTGATG	AGTGTGTACG	TCGTGAGACT	GCTCAGGTCT	TTCTTTTATG	TCACGGAGAC	CACGTTTCAA	21700
	AAGAACAGGC	TCTTTTCTTA	CCGGAAGAGT	GTCTGGAGCA	AGTTGCAAAAG	CATTGGAATC	AGGTACTGTA	21770
	TCCCCACGGC	AGGCCTCTGC	TTCTCGAAGT	CCTGGAACAC	CAGCCCGGCC	TCAGCATGCG	CCTGTCTCCA	21840
	CTTGCCCTGG	CTTCCCTGGC	TGTGCAGCTC	TGGGCTGGGA	GCCAGGGGCC	CCGTACAGG	CCTGGTCCAA	21910
	GTGGATTCTG	TGCAAGGCTC	TGACTGCCTG	GAGCTCACGT	TCTCTTACTT	GTAAATCAG	GAGTTTGTGC	21980
	CAAGTGTGCT	CTAGGGTTTG	TAAAGCAGAA	GGGATTAAAA	TTAGATGGAA	ACACTACCAC	TAGCCTCCTT	22050
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10	TGTTGGCCAG	GCTGGAGTGC	AGTGGCATAA	TCTTGGCTCA	CTGCAACCTC	CACCTCCTGG	GTTTAAGCGA	22190
	TTACACAGCC	TCAGCCTCCT	AAGTAGCTGG	GATTACAGGC	ACCTGCCACC	ACGCTGGCT	AATTTTCTGA	22260
	CTTTTAGGAG	AGACGGGGTT	TCACCATGTT	GGCCAGGCTG	GTCTCGAACT	CATGACCTCA	GGTGATCCAC	22330
	CCACCTTGGC	CTCCCAAAGT	GCTGGGTTTA	CAGGCTAAGC	CACCGTGCCC	AGCCCCCGAT	TCTCTTTTAA	22400
	TTCATGCTGT	TCTGTATGAA	TCTTCAATCT	ATTGGATTTA	GGTCATGAGA	GGATAAAATC	CCACCCACTT	22470
15	GGGCACTCAC	TGCAGGGAGC	ACCTGTGCAG	GGAGCACCTG	GGGATAGGAG	AGTTCCACCA	TGAGCTAACT	22540
	TCTAGGTGGC	TGCATTGAA	TGGCTGTGAG	ATTTTGTCTG	CAATGTCTCG	CTGATGAGAG	TGTGAGATTG	22610
	TGACAGATTG	AAGCTGGATT	TGCATCAGTG	AGGGACGGGA	GGGCTGGTCT	GGGAGATGCC	AGCCTGGCTG	22680
	AGCCCAAGGC	ATGGTATTAG	CTTCTCCGTG	TCCCGCCAG	GCTGACTGTG	GAGGGCTTTA	GTGAGAAAGT	22750
	CAGGGCTTCC	CCAGCTCCCC	TGCACACTCG	AGTCCCTGGG	GGGCTTGTG	ACACCCCATG	CCCCAAATCA	22820
20	GGATGTCTGC	AGAGGGAGCT	GGCAGCAGAC	CTCGTCAGAG	GTAACACAGC	CTCTGGGCTG	GGGACCCGAC	22890
	CTGTGTGCTG	GGGCCATTTC	CTTGATCTCG	GGGGAGGGTC	AGGGCTTTCC	CTGTGGGAAC	AGTTTAATAT	22960
	ACAATGCACG	TACTTAGAC	TTTACACGTA	TTTAATGGTG	TGCGACCCAA	CATGGTCATT	TGACCAAGTAT	23030
	TTTGGAAAGA	ATTAAATTGG	GGTGACCGGA	AGGAGCAGAC	AGACGTGGTG	GTCCCCAAGA	TGCTCCTTGT	23100
	CACACTGGGG	ACTGTTGTTT	TGCCCTGGGG	GCCTTGGAGG	CCCTCTCTCC	CTGGACAGGG	TACCGTGCCT	23170
25	TTTCTACTCT	GCTGGGCTG	CGGCTCTCGG	TCAGGGCACC	AGCTCCGGAG	CACCCGCGGC	CCCAGTGTCC	23240
	ACGGAGTGCC	AGGCTGTGAG	CCACAGATGC	CCAGGTCAG	GTGTGGCCCC	TCCAGCCCCC	GTGCCCCCAT	23310
	GGGTGTTTTT	GGGGGAAAG	GCCAGGGCCA	GAGGTGTGAG	GAGACTGGTG	GGCTCATGAG	AGCTGATTCT	23380
	GCTCCTTGCG	TGAGCTGCCG	TGAGCAGCCT	CTCCCGCCCT	CTCCATCTGA	AGGGATGTGG	CTCTTTCTAC	23450
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30	GGAGGGGCTC	GGGTTACAGT	GGGCCACAGT	GCAGCCTGGG	ACCAGGCTCC	CTGGTGCTGA	TGGTGGGACA	23590
	GTACCCCTGG	GGGTTGACCG	CCGCACTGGG	CGTCCCGAGG	GTGACTATA	GGACCAAGTG	TCCAGGTCCT	23660
	CTGCAAGTAG	AGGGGCTCTC	AGAGGCTCTC	GGCTGGCATG	GGTGGACGTG	GCCCCGGGCA	TGGCCTTCAG	23730
	CGTGTGCTGC	CGTGGGTGCC	CTGAGCCCTC	ACTGAGTCCG	TGGGGGCTTG	TGGCTTCCCG	TGAGCTTCCC	23800
	CCTAGTCTGT	TGTCTGGCTG	AGCAAGCCTC	CTGAGGGGCT	CTCTATTGCA	GACAGCACTT	GAAGAGGGTG	23870
35	CAGCTCGGGG	AGCTGTGCGA	AGCAGAGGTC	AGGCAGCATC	GGGAAGCCAG	GCCCCGCCCT	CTGACGTCCA	23940
	GACTCCGCTT	CATCCCCAAG	CCTGACGGCC	TGCGGCGCAT	TGTGAACATG	GACTACGTGC	TGGGAGCCAG	24010
	AACGTTCCGC	AGAGAAAGAG	GGGTGGTGTG	GCCTTGGTTT	AACCTTCTTT	TTAAACAGAA	GTGCGTTTGA	24080
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40	CACGGGCCCA	ACCCATTGTT	GGCACAAGTG	AGGTGGCCGA	GGTGGCCGTT	CCTCCAGAAA	AGCAGCGTGG	24220
	GGGTGTAGGG	GGAGCTCCTG	GGGCAGGGAC	AGGCTCTGAG	GACCACAAGA	AGCAGCGGGG	CCAGGGCCTG	24290
	GATGCAGCAC	GGCCCCGAGT	CCTGGATCCG	TGTCCTGCTG	TGGTGGCCAG	CCTCCGTGGC	CTTCCGCTTA	24360
	CGGGGCCCGG	GGACACGGCC	ACGACTGCCA	GGAGCCACCC	GGGCTCTGAG	GATCCTGGAC	CTTGCCCCAC	24430
	GGCTCTGTCA	CCCCACCCCT	GTGGCTGGGG	TGGCTCGGCT	GACCCCGTCA	TCTGAGGAGA	GTGTGGGGTG	24500
45	AGGTGGACAG	AGGTGTGGCA	TGAGGATCCC	GTGTGCAACA	CACATGCGGC	CAGGAACCCG	TTTCAACAG	24570
	GGTCTGAGGA	AGCTGGGAGG	GGTCTAGGTT	CCCGGGTCTG	GGTGGCTGGG	GACACTGGGG	AGGGGCTGCT	24640
	TCTCCCTTGG	GTCCCTATGG	TGGGGTGGGC	ACTTGGCCGG	ATCCACTTTC	CTGACTGTCT	CCCATGTGTT	24710
	CCCCGCCAGG	CCGAGCGTCT	CACCTCGAGG	GTGAAGGCAC	TGTTACGGCT	GCTCAACTAC	GAGCGGGGCG	24780
	GGCGCCCCGG	CCTCCTGGGC	GCCTCTGTGC	TGGGCTGGGA	CGATATCCAC	AGGGCCTGGC	GCACCTTCGT	24850
50	GCTGCGTGTG	CGGGCCGAGG	ACCCGCCGCC	TGAGCTGTAC	TTTGTCAAGG	TGGGTGCCGG	GGACCCCGCT	24920
	GAGCAGCCCT	GCTGGACCTT	GGGAGTGGCT	GCCTGATTGG	CACCTCATGT	TGGGTGGAGG	AGGTACTCCT	24990
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	TTACAGCCTT	CCTGCAGCAC	ATGGGGCCGA	CTGTGCACCC	TGACTGCCCG	GGCTCCTATT	CCCAAGGAGG	25130
	GTCCCACTGG	ATTCCAGTTT	CCGTCAGAGA	AGGAACCCGA	ACGGCTCAGC	CACCAAGGCC	CGGTGCCCTT	25200
55	CACCCCACTG	CTGAGCCAGG	GGTCTCTGTT	CCTGAGGCTC	AGAGAGGGGA	CACAGCCCGC	CCTGCCCTTG	25270
	GGGTCTGGAG	TGGTGGGGGT	CAGAGAGAGA	GTGGGGGACA	CCGCCAGGCC	AGGCCCTGAG	GGCAGAGGTG	25340
	ATGCTGTAGT	TCTGCGGTGG	CCACTGTGAG	TCTCCTCGCC	TCCACTCACA	CAGGTGGATG	TGACGGGGCG	25410
	GTACGACACC	ATCCCCCAGG	ACAGGCTCAC	GGAGGTCATC	GCCAGCATCA	TCAAACCCCA	GAACACGTAC	25480
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60	TAAAGTTTAC	GTGTGATAGT	CGTGTCCAGG	ATGTGTGTCT	CTGGGATATG	AATGTGTCTA	GAATGCAGTC	25620
	GTGTCTGTGA	TGCGTTTCTG	TGGTGGAGGT	ACTTCCATGA	TTTACACATC	TGTGATATGC	GTGTGTGGCA	25690
	CGTGTGTGTC	GTGGTGCAATG	TATCTGTGGC	GTGCATATTT	GTGGTGTGTC	TGTGTGTGGC	ACGTGTGTGT	25760
	CCATGTTGTG	TGTGCTCTGT	GTGTGCATGT	GTGTGTGTCT	GTGACACCTG	CATGTTCTAT	CTGTGTGTGT	25830
	CATGTTCTGT	ATGTGCCAT	TTGTGGTGTG	TGTGTGATG	TGTCCGTGAC	ATATGCGTGT	CTATGGCATG	25900
	GGTGTGTGTG	GGCCCTTGGC	CTTACTCTTT	CCTCCTCCAG	GCATGTTCCG	CACCATTTGT	CTACGCTCT	25970
65	GGGGTGTCTG	TTTGGGGAGC	TCCACATTCA	GGGTCTCTAC	TTCTAGCATG	GGTGGCCCTG	TCCTGTCAAC	26040
	GGGCTGGGCC	TTGAGACTG	TAAAGCCAGG	TTGAGAGGAG	AGTAGGGATG	CTGGTGGTAC	CTTCTGTGAC	26110
	CCCTGGCACC	CCGAGGACCC	CAGTCTGGCT	TATGCCGGCT	CCATGAGATA	TAGGAAGGCT	GATTGAGGCC	26180
	TGCGTCCCCG	GGACACACTC	CTCCAGAGGC	GGCCCGGGGC	CTTGGGGGCT	GGCAGGGGCT	AAAGGGGGCC	26250
	TGGGCTTGGG	TTCCACCCCA	GTGGTCAATG	GCACGCTGGA	GGGGTAAGCC	CTCAAAGTCC	TGCCAGGGCC	26320
70	GGGTGCAGAG	GTGAAGAAAT	ATCCCTCCAG	CTTCCGTCTG	GGGAGAGGCA	CATGTGGAAA	CCCACAAGGA	26390
	CCTCTTCTCT	TGACTTCTTGT	AGCT					26414

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Contig 2:

	TGTGGGATTG	GTTTTTCATGT	GTGGGATAGG	TGGGGATCTG	TGGGATTGGT	TTTTATGAGT	GGGGTAACAC	70
	AGAGTTCAAG	SCGAGCTTTC	TTCTGTAGT	GGGTCTGCAG	GTGCTCCAAC	AGCTTTATTG	AGGAGACCAC	140
	ATCTTCCTTT	GAAGTATGGT	CGGGTTTATA	GTAAGTCAGG	GGTGTGGAGG	CCTCCCTCGG	GCTCCCTGTT	210
5	CTGTTTCTTC	CACCTCTGGG	TCGTGTGGTG	CCTGCTGTGG	TGTGTGGCCG	GTGGGCAGGG	CTTCCAGGCC	280
	TCGTTGTGTT	CATTGGCCTG	GATGTGGCCC	TGGCTACGCT	CCGTCTCTGG	AATTCCTCTG	CGAGTTGGAG	350
	GCCTTCCTTC	TTCTCTTTT	TCCTCTTTT	TTTTTTTTT	TGATAACAGA	GTCTCGCTCT	TTTTGCCCA	420
	GGCTGGAGTG	GTTTGGCGTG	ATCTTGGCTC	ACTGCAACCT	GTGCTTCTGT	AGTTCAAGCA	ATTCTCTTGC	490
	CTCAGGCTCC	CAAGTAGCTG	GAATTATAGG	CGCCACCAC	CATGCTGACT	AATTTTGTGA	ATTTTAGTAG	560
10	AGACGAGGTT	TCTCCATGTT	GGCCAGGCTG	GTCTCGAACT	CCTGACCTCA	GGTGATCCTC	CCACCTCGGC	630
	CTCCCAAAGT	GCTGGGATGA	CAGGTGTGAA	CCGCCGCGCC	CGGCCGAGAC	TCGCTTCCGT	CAGCTTCCGT	700
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15	TCGGGCTCCT	TGAAGGAAAA	GTTCGATTA	TGGATGTTTG	AACCTTCTTT	TCTAAACAAG	CATCTGAAGT	980
	TGCCGTTTTC	CCTCTAAAGC	AGGGATCCCG	AGGCCCTTGC	CTGTGGAGTG	GCACCCGCTC	GGGGCTGTT	1050
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	TCTCAGATCA	GCAAGTGGAT	CGGGTGTGCA	GAGGCGCACA	CACCCCTACTG	AGAAGCTGTG	GTGAGAGGGG	1190
	TCTAGATTCT	GTGCTCCTTA	TGGGAATCTA	ATGCTGTATG	ATCTGAGGTG	GAACCGTTTG	CTCCCAAAAC	1260
20	CATCCCTCTC	CCCACTGTGT	TCCTGTGGAA	AAATCGTCTT	CCACGAAACC	AGTCCCTGGT	ACCACAATGG	1330
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25	TTCTCAGGGT	TGAATCGTAC	TCGATGTGGT	TTTAGCCAC	GGCCTTCCCG	CCAGCTCCTG	GGGGTGGGG	1610
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	TGTAGTGTG	TGTACAGTGC	CTGCTCACAT	CCTGTCTTGG	GGACGACAGG	GCTTAGCAGG	TCGGGTAGTA	1750
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30	CCGGGAGCTC	GAGTGCCACT	TGTGCCACGT	GACTGTGGAT	GGCAGTGGGT	CACGGGGGTC	TGATGTGTGG	1960
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35	TGTGGTGACT	GTGGATGGCG	GTGCTGGGGT	CTGATGTGTG	GTGACTGTGG	ATGGCGGTGC	TGGGTCTGTA	2380
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45	GTGGTGACTG	TGGATGGCAG	TCGTGGGGTC	TGATGTGTGG	TGACTGTGGA	TGGCGGTCTG	GGGTCTGATG	3010
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50	GTGCTGATGT	TGTGGTGACT	GTGGATGGCG	GTGCTGGGGT	CTGATGTGGT	GACTGTGGAT	GGCGGTCTGT	3430
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	GGGTCTGATG	TGTGGTGACT	GTGGATGGCG	GTGCTGGGGT	CTGATGTGGT	GACTGTGGAT	GGCGGTCTGT	3570
	GGGTCTGATG	TGTGGTGACT	GTGGATGGCG	GTGCTGGGGT	CTGATGTGGT	GACTGTGGAT	GGCGGTCTGT	3640
	GGGTCTGATG	TGTGGTGACT	GTGGATGGCG	GTGCTGGGGT	CTGATGTGGT	GACTGTGGAT	GGCGGTCTGT	3710
55	GAAGCTTCCC	AGGCGCTCTC	TGGGCTTCA	CCCGCATCG	GGCTTGGCCG	CAGGTCCACA	CGTCTGATC	3780
	GGAGAAACA	AGTGCCACG	TCTGGCCGGG	GCAGGCCACA	TTTGTGGCTC	ATGCCCTCTC	CTCTGCCCGC	3850
	AGGTCTCTAC	CTTGACAGAC	CTCCAGCCGT	ACATGCCACA	GTTCGTGGCT	CACCTGCAGG	AGACCAGCCC	3920
	GCTGAGGGAT	CGCGTCTCTA	TCGAGCAGT	CTGGGCACTG	CCCTGCAGGG	TTGGGCACGG	ACTCCACAGA	3990
	GTGGGTCTCT	CCCTGGGCAA	TCAGTGGGCT	CATGACCGGA	CAGACTGTGT	GCCTTGGGGG	GCACTGGGGG	4060
60	GAATGAGCTG	TGATGGGGGC	ATGATGAGCT	GTGTGCTTGG	GCGAAATCTG	AGCTGGGCCA	TGCCAGGCTG	4130
	CGACAGCTGC	TGCATTACAG	CACCTGCTCA	CGTTGACTGT	CGCGGCTCTC	CTCCAGTTCC	GCACTGGGGG	4200
	TGTTCAATGAT	TTGCTAAATG	TCTTCTCTGC	CAGTCTTGAT	CTTGAGGCCA	AAGGAAGAGT	GTCCCTCTCC	4270
	TTTAGGAGGG	CAGGCCATGT	TTGAGCCGTT	TCCTGCCCCG	CTGGCCCTCT	AGTGCTGGGT	CTGAGGCCAA	4340
	AGGAACGCTG	TCGCCCTTCT	TAGGAGGACG	GGCGGTCTTT	GAGCCACGCG	CCGCTGAGCG	GGCTCTCTAG	4410
65	TGCTGGGTCT	GTCCAGGTGG	CCCTGTGGCC	CTTTGACAGT	GTGGTCTGTC	CACGTGGCCC	TGTGGCTCTT	4480
	TGCAGATGCC	TGTTAGCACT	TGCTGGGCTC	TAGGGGACAG	TCGTGTCCAC	CGCATCAGGC	TCAGAGACCT	4550
	CTGGGCTGAT	TTCCCTTGGT	CCCAGGGTGG	GGGTGAGAGT	GGCTTGGGCT	GCTGGGACCT	AGACCTCTGT	4620
	CCCGGAGCTG	GGGACGCAAC	TGCTGGATCA	CATATGCCAT	CCGGGCCACG	GTGGGTCTGT	TGGGTGTGAG	4690
	CCAGCTTGGT	CCACAGGGTG	CGCCAGAGGA	GACGTTCTGT	GTACACACT	CTGCCCTAAG	CCATGTGTGT	4760
70	CTGCAGAGAC	TCGGCCCGGC	CAGGCCACGA	TGGCCCTGCA	TTCCAGCCCA	GCCTCCGACT	TCATCAGAAA	4830
	CAGTACGCCC	AAAAGGGACG	GAGGGTCTTG	GCCAGCTGGT	CCTGCTCTGC	TCAGCAACCA	CCGGCTCTAG	4900
	CCCATGTGTC	TCGCCCTCTG	TTTCCGAGAG	CTCCTGCTGT	AATGAGGCCA	GCACTGGGCT	TTTCCAGCTC	4970
	TTCTACGCTC	TCATGTGCCA	CCACGCGCTG	CGCATCAGGG	GCAAGTGAAT	CAGGTGSCCA	GTGCTCTCTT	5040
	CCCTGCGGGT	GGCTGGGCGG	GCTGGCAGGG	CTTCTGTGCA	CCTCTCTCTT	CCCTCTTCCC	AGGCTCCCGA	5110
75	CTGGGCGGGG	CCACAGAGGT	CTCCTTTTCT	GGCCCGCGCC	CCCTGCGGCT	CCTGGGCTGC	AGGCTCCCGA	5180
	GGCCCGGGAA	ACATGGCTCG	GCTTGGGCGA	GGCCGAGCGG	AGCAGGTGCC	ACACGAGGCC	TGGAAATGCG	5250
	AAGCGGGGTG	TGGAGTTGCT	CGTGGCTGGA	GGACGAGGGG	CGGGGGGTGT	GTCTGGCTCA	GGTGTGGGGG	5320

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	GAGCGTTTGA	GCCTGCAGCT	TGTCAGCTCC	AAGTTACTAC	TGACGCTGGA	CACCCGGCTC	TCACAGCCTT	5320
	GTATCTCTCT	CTCCCGATAC	AAAAGGATTT	TATCCGATTC	TCATTCTCTGT	CCCTGTCTGTG	TGACCCCGCG	5390
	GAGGGCGCGG	GCTCTTCTCT	CTGTGACTAG	ATTTCCCATC	TGGAAAGTGC	GGGGTTGACC	GTGTAGTTTG	5460
5	CTCCTCTCGG	GGGGCTCTGT	GTGGCCATGG	GGCAGGCGGC	CTGGGAGAGC	TGCCGTCACA	CAGCCACTGG	5530
	GTGAGCCACA	CTCACGGTGG	TAGAGCCACA	GTGGCTGGTG	CCACATCACG	TCCTCTGGAT	TTTAAGTAAA	5600
	ACCACACACC	TCCCGGCGAG	CATCTGCCCTG	CGACCCCTGTG	TGTGCCCTGGG	GAGAGTGGTA	GCACGGAGGA	5670
	AAATCGTGCA	CACCTCAAGT	CATCAGCAAG	GTCCATCCGCA	GTCAGGTGGA	ACGTGGAGGC	CTCTCTCTGG	5740
	GATCGTCTCC	AGCGGATAAA	GGACTGTGCA	CAGCTTCGGA	AGCTTTTATT	TAAAAATATA	ACTATTAATT	5810
	ATTGCATTAT	AAGTAATCAC	TAATGGTATC	AGCAATTATA	ATATTTATTA	AAGTATAATT	AGAAATATTA	5880
10	AGTAGTACAC	ACGTTCTGGA	AAAACACAAA	TTGCACATGG	CAGCAGAGTG	AATTTTGGCC	GAGGGACACG	5950
	TGTGCACATG	TGTGTAAGCG	GCCTCCAGGC	CCACAGAAAT	CGCTGACAAA	GTCACTCCCC	CAGAGAAGCC	6020
	ACCACGGGCG	TCCTTCGTGG	TCGTGAATTT	TATTAAGATG	GATCAACTCA	CGTACCGTCC	ACGTGTGGCA	6090
	GGGCTTTGGG	GAATGTGAGG	TGATGACTGC	GTCTCATGTC	CCTGACAGAC	AGGAGGTGAC	TGTGTCTGTG	6160
	CTGTCCCTAG	GACACGGACA	GGCCCGAAGC	TCTAGTCCCC	ATCGTGGTCC	AGTTTGGCCCT	CTGAATAAAA	6230
15	ACGTCCTCAA	AACCTGTTGC	CCCAAAAATC	AAGAACAGAG	AGAGTTTCCC	ATCCCATGTG	CTCACAGGGG	6300
	CGTATCTGCT	TGCGTTGACT	CGCTGGGCTG	GCCGGACTCC	TAGAGTTGGT	GGGTGTGCTT	CTGTGCAAAA	6370
	AGTGCAGTCC	TCCTGGCCAT	CACCTGTGTA	TCTGCACACG	CARGGAAAGC	CTCTTTTCTT	TTCTTTCTTT	6440
	TTTTTTTTTT	GAGACGGAAAC	GTCACTGTTG	TCTGCCCTGGG	CTTGAGTGCA	GTGGCGCGAT	CTCAACTCAC	6510
20	TGCAACCTCC	GCCTCCCGGG	TTCCAGCATT	TCTCCTGCCT	CAGCCTCCCG	AGCAGCTGAG	ATTACAGGCA	6580
	CCCACCCCTT	CGCGCTGGCT	AATTTTTGTA	TTTTTAGTAG	AGAGGGGTTT	TTGCCATGTT	GGCCAGGCTG	6650
	GTCTCGAATC	CCTGACCTCA	GGTGATCCAC	CCACTCCGGC	CTCCCAAAGT	GCTGGGATTA	CAGGTGTGAG	6720
	CCATCAGCGC	CAGCCGGAAA	GCCTCTTTTT	AAGGTGACCA	CCTATAGCGC	TTCCCGAAAA	TAACAGGTCT	6790
	TGTTTTTGCA	GTAGGCTGCA	AGCGTCTCTT	AGCAACAGGA	GTGGCGTCC	GTGGGCTCTG	GGGATGGCTG	6860
	AGGGTCGCGT	GGCAGCCATG	CCTTCTGTGT	GCACCTTTAG	GTTCACCGGG	GCTATTCTGC	TCTACTGTTT	6930
25	TGTCTGAAAA	CGCACCCTTG	GCATCCTTGT	TTGGAGAGTT	TCTGCTTCTC	GTGGTCTATG	CTGAAACTAG	7000
	GGGCAAGGTT	GTATCCGTTG	GGCGCAGCGC	GCTACATGTA	GGGTCTAGAG	TCTTTACCGG	TGGACAAATT	7070
	CCTTGA AAAA	AAAAAAGGA	GTCCGGTTAA	GCATTCATTC	CGGGTCAAGT	GTCTGGTTCT	GTGAATAAAC	7140
	TCTAAGATTT	AAGAAACCTT	AATGAAGAA	AACCTTGATG	ATTACAGGCA	AGGATGTGGT	CACACCTGTG	7210
	GCTGGATCTG	TTTCAGCCGC	CCCAGTGCAT	GGTGAGAGTG	GGGAGCAGGG	ATTGTTTGTG	CAGAGGTCTC	7280
30	ATCTGGTATG	TTTCTGAGGT	GTTCGCCGGC	TGAATGGTAG	ACGTGTCTGT	TGTGTGTATG	AGGTTCTGTG	7350
	TCTGTGTGTG	GCTCGGTTTG	AGTGTACGCA	TGTCCAGCAC	ATGCCCTGCC	CGTCTCTCAC	CTGTGTCTTC	7420
	CCGCCCCAGG	TCCTACGTCC	AGTGCCAGGG	GATCCCGCAG	GGCTCCATCC	TCTCCACGCT	GCTCTGCAGC	7490
	CTGTGCTACG	CGGACATGGA	GAACAAGCTG	TTTGGCGGGA	TTCCGGCGGA	CGGGTGAAGC	CTCCTCTTCC	7560
35	CCAGGGGGGC	TTGGGTGGGG	TGTGATTTGC	TTTTGATGCA	TTTCAAGTTA	ATATTCTTGG	TGCTCTGGAG	7630
	ACCATGACTG	CTCTGTCTTG	AGGAACAGGA	CAAGGTGTGA	GCCCTCTCTT	GGTATGAAGC	CGCAGGGGAG	7700
	GGGTTGCACA	GCCTGAGGAC	TCCGGGCTCC	ACCGAGGCTC	TGTCCAGCGG	CCATGTCCAG	AGGCCCTCAGG	7770
	ECTCAGCAGG	CGGGAGGGCC	GCTGCCCTGC	ATGATGAGCA	TGTGAATTCA	ACACCGAGGA	AGCAGCCAG	7840
	CTTCTGTGAC	GTCAACCAGG	TTCCGTTAGG	GTCTTGGGG	AGATGGGGCT	GGTGCAGCCT	GAGGGCCCCA	7910
	ATCTCCCGAG	AGGCCCTCGA	CAGGTGGGCT	GGACTGGGCG	CCTCTTCAGC	CCATTGCCCA	TCCCACTTGC	7980
40	ATGGGGTCTA	CACCCAAAGG	CCACACACCC	TAATATCTGT	GCCAACTTAA	TGTGGTTCAA	CTCAGCTGGC	8050
	TTTTATTGAC	AGCAGTTACT	TTTTTTTTTT	TAATACTTTA	AGTTCTAGGG	TACATGTGCA	CGACGTGCAG	8120
	GTATAGTTACA	TATGTATACA	TGTGCCATGT	TGGTGTGCTG	CACGCAATTA	CTCATCATTT	ACATTAGGTA	8190
	TATCTCTCAA	TGCTATCCCT	CCCCACTCCC	CCCATCCCAT	GACAGGCCCT	GGTGTGTGAT	GTTCGCCACC	8260
45	CTGTGTCGAA	GTGTTCTCAT	TGTTCAAGTT	CCACCTGTGA	GTGAGAACAT	GTGGTGTGTT	TGTTTCTTTC	8330
	CTTGCAATAG	TTTGCTCAGA	GTGATGGTTT	CCAGCTTCGT	CCATGTCCCT	ACAAAGGACA	TGAATCATTC	8400
	CTTTTTATAG	ACTGCATAGT	ATTCGCTGGT	GTATATGTGC	CACATTTTCT	TAATCCAGTC	TATCATCGAT	8470
	GGACATCTTG	GTGGTTTGCA	AGTCTTTGCT	ACTGTGAATA	GTGCCGCAAT	AAACATACGT	GTGATGTGTG	8540
	CTTTATAGCA	GCATGATTTA	TAATCCTTTG	GGTATATACC	CAGTAATGGG	ATGGCTGGGT	CAAAATGGAT	8610
	TTCTAGTTCT	AGATCCTTGA	GGAAATCACA	CACGTCTTTC	CACAATGGTT	GAAGTAGTTT	CACTCTCCAC	8680
50	CAACAGTGTA	AAAGTGTCTT	GGTGCTGGAG	AGGATGTGGA	CAGCAGTTAT	TTTTTTATGA	AAATAGTATC	8750
	ACTGAACAGG	CAGACAGTTA	GTGAAGGATG	CGTCAGGAAG	CCTGCAGGCC	ACACAGCCAT	TTCTCTCGAA	8820
	GACTCCGGGT	TTTTCTGTG	CATCTTTTGA	AACTCTAGCT	CCRAATTATG	CATGTACAGT	GATCAAGGTT	8890
	TCTTCTTCAT	TAAAGTTCAA	GTCTAGATT	GAATAAGTT	TATGTAACAG	AAACAAAAT	TTCTTGATCA	8960
	CACAACCTGC	TCTGGGATTT	GGAGGAAAGT	GTCTTCGAGC	TGGCGGCACA	CTGGTCAGCC	CTCTGGGACA	9030
55	GGATACCTCT	GGCCCATGGT	CATGGGGCGC	TGGGCTTGGG	CCTGAGGGTC	ACACAGTGCA	CCATGCCCGA	9100
	CTTCCTGTGG	ATAGGATCTG	GGTCTCGGAT	CATGCTGAGG	ACCACAGCTG	CCATGTCTGT	AAAGGGCACC	9170
	ACGTGGGTCA	GAGGGGGCGA	GGTTCGCCAG	CCAGCTTTC	TTACCGTCTT	CAGTTATTTT	TCCCTAAGAG	9240
	TCTGAGAAGT	GGGGCCGCGC	CTGATGGCCT	TCGTTCTGCT	TCAGCTGGCA	CAGAATTGCA	CAAGCTGATG	9310
60	GTAACACTG	AGTACTTATA	ATGAATGAGG	AATTGCTGTA	GCAGTTAACT	GTAGAGAGCT	CGTCTGTTGG	9380
	AAAGAAATTT	AAGTTTTTCA	TTTAAACGCT	TTGGAGAATG	TTACTTTTAT	TATGGCTGTG	TAAATTTGTT	9450
	GACATTCACT	CCCTCGTAGA	CAGATACTAC	GTA AAAAGTG	TAAAGTTAACT	CTTGCTGTGT	ATTTTCCCTT	9520
	ATTTTAGGCT	GCTCCTGCGT	TTGGTGGATG	ATTTCTTGTT	GGTGACACCT	CACCTCACCC	ACGCGAAAGC	9590
	CTTCTCTCAG	TGAGGCCCGT	GCCGTGTGTC	TGTGCGGACC	TCCACAGCCT	GTGGGCTTTG	CAGTTGAGCC	9660
65	CCCCGTGTCC	TGCCCTGGGC	ACCGCAGCGT	TGTCTCTGCT	AAGTCTCTCT	TCTCTGCCGG	TGCTGGATCC	9730
	CCAAGAGCAG	AGGGCGTTGG	CGGTGCACCC	AGCCCTGGGG	GCGCAGGGGC	ACCTTCGGGA	GGGAGTGGGT	9800
	ACCGTGCAGG	CCGTGCTCCT	GCASAGACGC	ACCCAGGTTA	CACACGTGGT	GAGTGCAGGC	GGTGACCTGG	9870
	CTCCTGCTGC	TCTTTGGAAA	GTCAAGAGTG	GCGGCTCTCT	GGGCCCCAGT	GAGACCCGCA	GGAGCTGTGC	9940
	ACAGGGCGCT	CAGGGCGGAG	GCGGCAGCCT	GCTCCGAGG	GTGCACCTGA	GCTGCGGAG	AGCAGGAGCT	10010
	GCTGAGTGAG	CTGGGCCACA	CGGTTCGCTG	CGGTACGTTT	CCTGCGTGGG	GTGTTTGGG	ATCGGTGGGA	10080
70	GAATTTGGAT	TTGCTGAGTG	CTGCTGTCTT	GAATTAAGGA	GATGGCTAGG	AGTGGGTTT	AGAGTTGATT	10150
	TTTGTGAATC	AAACTAAAT	CAGGCCAAGG	GGAGTGTGCT	TCAGCACAGG	GGATTGTGCA	ATGTGGTCCC	10220
	CCTCAAGGGC	GCCCCACAGA	GTCGGTTCGC	TGTGTTTAAA	GTGCGATTG	ACGAGGGAGC	AGAAACCTTG	10290
	AAAGCTGTAA	AGGGAACCCCT	CAGAAAATGT	GGCCGCGAGG	GGTGGTTTCA	SGTGGTTTGC	TGGGCTGTGT	10360
	TTGTGAAATC	CAATTTGGAC	CTGCCCTGCA	AGTCAACCTT	CCAGGTGCCC	CCTGCCAGGC	CGCCCTGGGC	10430
75	TGGGGGTATG	CCTGCCGTTT	CTGTGTCGCG	AGCCGCGAGG	ACAGCAGGCT	GTGCACATTT	AAATCCACTA	10500
	AGATTCTACT	GGGGGAGGCC	CAGGTGCGCA	GCAATGAGG	GCTCAGGAGT	CCTGAGGCTG	ATGAGGGGAG	10570
	AGAGCAGAGC	GGGAACGCTG	CTTCTGTGTC	GCAATTTCTT	GAGGGTCTGT	GCCAGGGAGG	TGGCTCAGAG	10640
	TGTATGTTGG	GGTCCCAACG	GTTGGCAAACT	TGTGCTCTG	ATGAGTCCGC	AGCATGTGTA	CAGGAAGGGG	10710

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	TGGCCACAGG	GAGCTGGGAA	TGCACCAGGG	GAGCTGCGCA	GCTGGCCGAG	GTCCACAGGC	CAGGCCACAG	10780
	GAAGGGCAGG	GGGACGCCCG	GGGCCACAGC	AGAGGCCGCA	GGAAAGGAAG	GGGATGCCCA	GGCCAGAGCA	10850
	GAGGCTACCG	GGCACAGGGG	GGCTCCCTGA	GCTGGGTGAG	CGAGGCTCAT	GACTCGGCCA	GGGAACCTCC	10920
	TTGACGTGAA	GCTGACGACT	GGTGTGGCCC	AGCTCACAGC	CCAGCCAGGT	CCCCGGCCTG	AGCAGGAATC	10990
5	CAGAAGCCCTC	CCCTTTGTCT	AAAGCAGAGC	AGATGCCCTC	AGGGCATCTA	GGAGAAAAAC	GGCAAGTCG	11060
	TTGAGAAACG	TCTTAAAGAG	AGGTGGGATG	GTGGCAATTT	CTTGTCCAGA	TTTTAGTCTG	CCCCGGACCA	11130
	CAGATGAGTC	TATAACGGGA	TTGTGGTGT	GCCATGGGGA	CACATGAGAT	GGACCATCAC	AGAGGCCACT	11200
	GGGGCTGCAC	CTCCCATCTG	AGTCTGGCT	GTCCCGGGTC	CAGGCCAGGT	TCTTGCATGC	TCACCTACCT	11270
	GTCTTGCCCG	GGAGACAGGG	AAAGCACCCC	GAAGTCTGGA	GCAGGGCTGG	GTCCAGGCTC	CTCAGAGCTC	11340
10	CTGCCAGGCC	CAGCACCCCTG	CTCCAAATCA	CCACTTCTCT	GGGGTTTTCC	AAAGCATTTA	ACAAGGGTGT	11410
	CAGGTTAAGCT	CCTGGGTGAC	GGCCCCGCAT	CCTGGGGCTG	ACATTGCCCC	TCTGCCTTAG	GACCTGGTCT	11480
	CGAGGTGTCC	CTGAGTATGG	CTGGCTGGTG	AACTTGGCGA	AGACAGTGGT	GAACCTCCCT	GTAGAAGAGC	11550
	AGGCCCTGGG	TGGCACGGCT	TTTGTTCAGA	TGCCGGCCCA	CGCCCTATTG	CCCTGGTGGC	GCCTGTGCTG	11620
	GGATACCCCG	ACCCTGGAGG	TGCAGAGCGA	CTACTCCAGG	TGAGCGCACC	TGGCCGGGAG	TGGAGCCTGT	11690
15	GCCCGGCTGG	GGCAGGTGGT	GCTGCAGGGC	CTTGTGCTCC	ACCTCTGCTT	CGGTGTGGGG	CAGGCGACTG	11760
	CCAATCCCAA	AGGGTCAGAG	GCCACAGGGT	GCCCCCTGCT	CCATCTGGGG	CTGAGCAGAA	ATGCATCTTT	11830
	CTGTGGGAGT	GAGGGTGTCT	ACAACGGGAG	CAGTTTTCTG	TGCTATTTTG	GTAAAAGGAA	ATGGTGCACC	11900
	AGACCTGGGT	GCACTGAGGT	GTCTTCAGAA	AGCAGTCTGG	ATCCGAACCC	AAGACGCCCG	GGCCCTGGTG	11970
	GGCGTGAGTC	TCTCAAACCC	GAACACAGGG	GCCCTGCTGG	GCATGAGTCC	CTCTGAACCC	GAGACCCCTG	12040
20	GGCCCTGCTG	GGCGTGAGTC	TCTCCGAACC	CAGAGACTTC	AGGGCCCTTT	TGGGCGTGAG	TCTCTCCGCT	12110
	GTGAGCCCCA	CACCTCCAGG	CTCATCCACA	GTCTACAGGA	TGCCATGAGT	TCATGATCAC	GTGTGACCCA	12180
	TCAGGGGACA	GGGCCATGGT	GTGGGGGGGG	TCTCTACAAA	ATTCTGGGGT	CTTGTTCGCC	CAGAGCCCGA	12250
	GAGCTCAAGG	CCCCGTCTCA	GGCTCAGACA	CAAAATGAAT	GAAGATGGAC	ACAGATGCAG	AAATCTGTGC	12320
25	TGTTTTCTTT	ATGAATAAAA	AGTATCAACA	TTCCAGGCAG	GGCAAGGTGG	CTCACACCTA	TAATCCACGC	12390
	ACTTTGGGAG	GGCCAGGTGG	GTGGATCACT	TGAGGCCAGG	AGTTTGAGGC	CAACCTAACC	AACATAGTGA	12460
	AATTCATTTT	CTACTTAAAA	AATACAAAAA	TTAGCCTGGC	CTGGTGGCAC	ACGCCGTGAG	TCCCGCTAT	12530
	GGGGGAGGCT	GAGGCAGGAG	AATCATTTGA	ACCCAGGAGG	CAGAGGTGGC	AGTGAGCCGA	GATCACACCA	12600
	CTGCACTCCA	CCCTGGGCAA	CAGAGTGAGA	CTTCATCTTA	AAAAAATAAA	AAAAAGTATC	AGCATTTCCA	12670
30	AACCATAGTG	GACAGGTGTT	TTTTATTCTT	GTCTTCTGAT	AAATTTTACT	GGTGTGTGTC	TAGAGGCCGG	12740
	AACTGGGGGT	GGCTTCCTCT	GAAGGGCACA	CTTTCATGGG	AAAGAGAAAT	AGTGGTGAAT	GGTTGTTAAA	12810
	CCAGAGGTTT	AAACTGGGGT	CCTGTCTGTC	TGAGTTAACA	GTCCAGATCT	GGACTTTGCG	TCTTTCCACA	12880
	ATGCTCCCTG	GGCTTTGCTT	CATGGGGGAG	CAGCAGGTGT	GGACACCCCT	GTGATGGGGG	AGCAGCAGGT	12950
	GCAGACGCCC	TCATATGGGG	GGAGTGGCAG	GTGCAGACAC	CCTTGTGCAT	GGTGCCACGC	ATGTCCCTGT	13020
35	TGCGACTGCC	TCCCCACAAG	GATGCCGGTC	TCCTGTGCTC	CCACAGTCCG	CTGCTTCCCT	CTCAGAGCCT	13090
	TACCTGGTCC	TGGCCTCCAC	TGGCTTTGTC	TGCATGATTT	CCACATTTCC	TGGGCTCCCA	GCACCTCTTC	13160
	GCCTCTCCCA	GGCACCTCTG	CAGTGTGCTC	CATACCAGTC	AGCTGTGAAC	TGTCCACTGC	TTATTTTGTG	13230
	CCCATGAAAA	TGTATTTTTT	AGGACAGGCA	CCCTGTGTTT	CAGCCTCTGG	CACAGCATCA	GTGAATGTTA	13300
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	GGCTAGTGCA	GGATGGGTGG	GCATCGAGTG	ATCAGATGTG	GGTCCAATGC	CAGAATATTG	TGTGCTCCCA	13440
40	AAGGCCACTT	GGTCAGAGTG	TGTGCTTGCA	GAGGTGGCTC	TAAAGGCTCA	GCAGTGGAGG	CAGTGGTTCG	13510
	CCATACTCAG	GGTGAACCTA	CATCCTCTGT	GTCTGAAGTA	TACAGCAGAG	GCTTGAAGGG	CATCTGGGAG	13580
	AAGAAAACAG	GCAAAATGAT	TAAGAAAAGT	GAAAAAGGAA	AAGTGGTAAG	ATGGGAATTT	TCTTGTCCAG	13650
	ATTTTAGTCT	CCCAAAACCA	AGCTCAGATG	GTAGAATGTG	GTGAGAACTG	ATGGACAGAA	CAATAGAGCA	13720
	AAACGGAGGC	CCTATCTCTC	AGAAACGTGT	GTTAATGTGG	TATGTGGCAC	AGCTGATGGA	AAAGAGAGTG	13790
45	TGTGTGTAAT	TTTTTTTTCT	GAGAAAACCT	ACTGGAAGCA	AATAAGTTGT	GTCTTACAG	CATATACCAG	13860
	AGGAGATTCT	AGGTAGAAGA	GGAGACACAT	GCAACACAAC	CCAGCAACAG	AAATAAAACA	AAAGACTCAA	13930
	AGGGAAGCCT	GGTGAACGTT	CCCTGGTTTT	GTGTTGGGGA	AGGACACACA	GGGAGGCCGA	TGAAGCCAGT	14000
	GAGGCACCGG	GCATTGCTTT	CACCTGCAGAG	AAACTCAGCT	TGCTTGAGCC	ACAGTGAAAA	TGGCCATTTC	14070
	CTGGAGCGTT	TGTGCACGTG	ATTTATTAA	GGCCCTCTGT	GAGGTCTCTG	ACATTCATCT	TCTCATTTTC	14140
50	TTCTCTTAAC	CACCTGAGAG	STAGAGGAGG	AAAGGCTCCA	GGGGAGCAGC	CGCCCTTGGT	CACCCAGCTG	14210
	GCAAAAGGGA	TGCATGATTG	CAGCCTGGCC	TCCTGTCTCC	GGGCCCTTGC	TCTGCCCGAG	GACCCACAGC	14280
	AAGTCAGACC	CATAGGCTCA	GGGTGAGCCG	GAGCCCAAGG	TGCTGTGGGG	GATGGCTGTG	AAAGAGAGAA	14350
	TGGACGTCTG	ATGCACACTT	GGGAAGSTCC	TACCAGCAGC	GTCAAGAGAA	TGCATGTGAA	ACTGACACGC	14420
	AGACCCATCC	CTCAAAGAAA	CGCAGCTGAA	AUTGATGGCG	AGACCTGTCC	CCATCCCTCA	TGCTGGCTCC	14490
55	TTTTCTGGGC	TTGCCAAGAG	CCAGCATCAG	GTGAGGCAA	GCTGGAAAGA	CTTTCTGGA	AAGCAGCTTG	14560
	TTTGCATGGA	AGTCTCTACA	ATGCTCTGTG	TCTTCCAGT	AAATCCACTT	CTGAAGTGAC	CAGACATTAT	14630
	CACGGGTCTT	ATTTACCAT	TCCAGTGTTC	CAGGCAGGGG	GACTTGCCAC	AGCAAGTCAC	GAACCTGCCC	14700
	AAATACAGGG	CTAAGGAGAT	ATTATGCATC	ACAAAACCTG	CTCTGCCATT	AAACATTTTT	CAAGAATTTT	14770
	TTGAAGAATG	TTTAATGGCA	CAAAACGTTT	ATTTCAATGT	AGCAATGTTC	AAAGCTGGAT	GTAAAAGAAC	14840
60	ACACCCACAG	AGCCTGCCGT	GAATGTGATG	TGTGTTTATC	TTTGSACATG	GACATACATG	GGCAGTGAGT	14910
	GGTGGTGAGG	CCCTGGAGGA	CATCGGTGGG	ATGCTCCAT	CCTGCCCTCC	TGGAGACACC	ATGTGTGCCA	14980
	CGTGCACTCA	CTGGAGCCCT	GTTTAGCTGG	TGCCACCTGG	CTCTTCCATC	CCTGAGATTC	AAACACAGTC	15050
	AGATTCCCCA	CGCCCAACTC	AGTGTTCCTC	CACAAAAAAC	CTGAGTCACA	CCTGTGTCCA	CTCGAGGAGC	15120
	GCCCGGGAGC	CAGGGCTCCA	CAGTTTATTA	TGTGTTTTTG	GCTGAGTTAT	GTGCAGATCT	CATCAGGACA	15190
65	GATGATGAGT	GCACAAACAC	GGCCGTGGGA	GTTTGGATA	CACCTAACAT	CACAGCCAG	GTCTGGTGG	15260
	AGTTTGGTCA	TGCAGAGTCT	GCATGGGATG	TAGCATTTGG	AGTCTATGGA	GTGAGCACGC	AGCCCGCTGG	15330
	GGCTGCAGCG	CATGCCCCAG	GCAGGACAGG	GAAGCGGGAG	GAAGCGAGGA	GGCTCTTTGG	AGCAAGGTTT	15400
	GCAGGAGGGG	GCTGGGTGTG	GGCAGGACAC	CTGTGTCTGA	CATTCCCCCC	TGTGTCTCAG	CTATGCCCTG	15470
	ACCTCCATCA	GAGCCAGTCT	CACCTTCAAC	CGCGGCTTCA	AGGCTGGGAG	GAACATGCTT	CGCAAGCTCT	15540
70	TTGGGCTCTT	GGCGCTGAAG	TGTCACAGCC	TGTTTCTGGA	TTTGCAGSTG	AGCAGGCTCA	TGGTCAGGAC	15610
	AGAGTTTCAGA	GTTCAGGAGG	TGTGTGCCCA	AGTATGTGTG	TGTGTGTGTG	CGCGCTGGCC	TGCAAGGTTG	15680
	ATGGTCACTG	GCTCCACGTA	AGAGTGCACA	TGTACGCATA	TACACGTGAG	CACATACATG	TGTGCATGTC	15750
	TGTACATGAA	GGCATGGCAG	TGTGTGCACA	GGCATGAAGT	TGTGCACATG	TGTGCACATG	GCAATGGATA	15820
	CCTGACATGC	ATGTTGTGTC	GTGCACAGTC	GTGTGGGCAT	TCACGTGAGG	TGCATGCGTG	TGGGTGTGTA	15890
75	GTGTGAGTAG	CATGTGTGCA	CATAACATGT	ATTGAGGGGT	CCTGTGTGTC	ACCCCGCTAG	GTCTTCACTA	15960
	CCAGTGCCAC	TCCTTACAGG	ATGACAGGGG	GTCCAGGCC	TTGGTGGGCT	GAGGCTCTCA	GTAGGAGGTC	16030
	CTGAGGGCAT	TGTCTCATCT	GGGCATCCGC	GTCCACTCCC	TCTCTGTGG	GCTTCTGTGT	CAACTCTCTG	16100
	TCTCTGTGG	GCAATTCATC	CCACTCAGCT	CCCTCTCTCC	TGTGGGCATC	CGCTCTCAT	CCCTCTCTCT	16170

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	GTGGGCATCT	GGGTCCACCT	CCCCCTCTG	TGGGCATTGG	CGTCCACTCC	CTCTCCTGGT	TCCTTCCTGT	16240
	CTTGGCCGAG	CCTCGGGGGC	AGGCAGATGA	CACAGAGTCT	TGACTCGCCC	AGGGTGGTTC	GCAGCTGCCG	16310
	GGTGAGGGCC	AGGCCGGATT	TCACTGGGAA	GAGGGATAGT	TTCTTGTCAA	AATGTTCCCT	TTTCTGTTC	16380
5	CATCTGAATG	GATGATAAAG	CAAAAAGTAA	AAACTTAAAA	TCCCAGAGAG	GTTTCTACCG	TTTCTCACTC	16450
	TTTCTTGGCG	ACTCTAGGTG	AACAGCCTCC	AGACGGTGTG	CACCAACATC	TACAAGATCC	TCCTGCTGCA	16520
	GGCGTACAGG	TGAGCCGCCA	CCAAGGGGTG	CAGGCCCAGC	CTCCAGGGAC	CCTCCGCGCT	CTGCTCAGCT	16590
	CTGACCCGGG	GCTTCACCTT	GGAACTCCTG	GGTTTATGGG	GCAGGAATG	TCTTACGTTT	TCAGTGGTGC	16660
	TGCTGCTGT	GCACAGTTCT	GTTCCGCTGG	CTCTGTGCAA	AGCACCTGTT	CTCCATCTCT	GGGTAGTGGT	16730
10	AGGAGCCGGT	GTGGCCCCAG	GTGTCCCCAC	TGTGCCCTGG	CAGTGGCCGT	GGGACGTCAT	GGAGGCCATC	16800
	CCAGGGCAGC	AGGGGCATGG	GGTAAAGAGA	TGTTTATGGG	GAGTCTTAGC	AGAGGAGGCT	GGGAAGGTGT	16870
	CTGAACAGTA	GATGGGAGAT	CAGATGCCCG	GAGGATTTGG	GGTCTCAGCA	AAGAGGGCCG	AGGTGGGTGC	16940
	AGGTGAGGGT	CGCTGGCCCC	ACCCCGCCGA	AGGTGCAGCA	GAGCTGTGGC	TCCCCACACA	GGCCGGCCAG	17010
	CACCTGTGCT	CTGGGCATGG	CTGTGCTCCT	GGAACTTTCC	CTGTCTGGC	TGCTCAGGGG	GTGCCCTGTC	17080
	CAAGAATCGA	CAACTTATAT	ACAGAGGGAA	GGGCCAATCT	GTGGAGGCCA	CAGGGCCAGC	TTCTGCCTGG	17150
15	AGTCAGGGCA	GGTGGTGCCA	CAAGCCTCGG	GGCTGTACCA	AAGGGCAGTC	GGGCACCA	GGCCGGGGCC	17220
	TCCACCTCAA	CAGGCCCTCC	GAGCCACTGG	GAGCTGAATG	CCAGGAGGCC	GAAGCCCTCG	CCCATGAGG	17290
	GCTGAGAAGG	AGTGTGAGCA	TTTGTGTAC	CCAGGGCCGA	GGCTGCGCGA	ATTACCGTGC	ACACTTGATG	17360
	TGAAATGAGG	TCGTCTCTA	TCGTGGAAAC	CCAGCAAGGG	CTCAGCGGAG	AGTTTTCCAT	TACAAGGTGC	17430
	TACCATGAAA	ATGGTTTTTA	ACCCGAGTGC	TTGGCCCTTC	ATGCTCTGGC	AGGGAGGGCA	GAGCCACAGC	17500
20	TGCATGTTAT	CGCCTTTGCA	CCAGCTCCAG	AGGCTTGGGA	CCAGGCTGTC	TCAGTTCCAG	GGTGGCTCGG	17570
	GCTCAGACCG	CGCTGCTCTC	TGCTTCTCT	CTCTGCCTCA	AATCTTCCCT	CGTTTGCTATC	TCCCTGACGC	17640
	GTGCTTGGGC	CCTCGTGCAA	GCTGTGTGAC	TCTTTCCCGG	AAACCCCTTG	GGTGTGCTGG	ATACAGGTGC	17710
	CACCTGAGGAC	TGGAGGTGTC	TGACACTGTG	GTTGACCCCA	GGTCCAGCT	GGCGTCTTG	GGCCCTCCTT	17780
	GGGCCATGAT	GAGGTCAGAG	GAGTTTTCCC	AGGTGAAAC	TCTTGGGAAA	CTCCAGGGCC	CATGTGACCT	17850
25	GCCACCTGCT	CCTCCCATAT	TCAGCTCAGT	CTTGTCTCA	TTTCCCCACC	AGGGTCTCTA	GCTCCGAGGA	17920
	GCTCCCGTAG	AGGGCCTGGG	CTCAGGGCAG	GGCGCTGAG	TTTCCCCACC	CATGTGGGGA	CCCTTGGGTA	17990
	GTGCTTGTAT	TGGGTAGCCC	TAGGAGGGCC	GAGATGCCAT	GGGCCACGGG	CGGTTTCCAA	ACACAGAGCT	18060
	AGGCACGTGG	AAGGCCCAGG	AATCCCTTC	CCTCGAGGCA	GGAGTGGGAG	AACGGAGAGC	TGGGCCCTCA	18130
30	TTTCACGGCA	GCCAGGCTGC	AGTGGGCGAG	GCTGTGGTGG	TCCACGTGGC	GCTGGGGGCG	GGGTCTGATT	18200
	CAAAATCCGT	GGGGCTCGGC	CTTCTGGGCC	CGTGTGGGCC	GGCCCTCCAC	ACGGGCTTGG	GGTGGACGCC	18270
	CCGACCTCTA	GCAGGTGGCT	ATTCTCTCCT	TTGGAAGAGA	GGCCCTCAAC	CATGCTAGGT	GTCTCCCTCC	18340
	TGGGTACGGA	CGGTGGCCGT	GTGGCAACCC	CGGGACCTTA	GGCTTATTTA	TTTGTTTAAA	AACATTCTGG	18410
	GCTTGGCTTC	CGTTGTGCT	AAATGGGGAA	AAGACATCCC	ACCTCAGCAG	AGTTACTGAG	AGGCTGAAC	18480
35	CGGGGCTCTG	GCTTGACTGG	TGTGATCTCA	GGTCATTCCA	GAAGTGGCTC	AGGAAGTCAG	TGAGACCAAG	18550
	TAGATGGGGG	GCTCAGGCG	TGGGTGAGAT	GAGGTACACG	GGGGGCTCAG	GCAGTGGGTG	AGGCCAGGTA	18620
	CATGGGGGGC	TCAGGCACTG	GGTGAGATGA	GGTACACGGG	GGGCTCAGGC	AGAGGGTCAG	AGGCTGATCA	18690
	CGGGGGCTCT	GATCAGACCC	ACATATGAGC	ACATGTGCAC	ATGTGCTGTT	TCATGTTAGC	CAGGTCTGTG	18760
	CACACCTGCC	CCAAAGTCCC	AGGAAGCTGA	GAGGCCAAAG	ATGGAGGCTG	ACAGGGCTGG	CGCGGTGGCT	18830
	CACACCTGTA	GTCCCAACAC	TTTGGAGGCG	CGAGGCGAGA	GGATCCCTTG	AGCCCAAGAG	TTTAAGACCA	18900
40	GCCTGAGCAA	CATAGTAGAA	CCCCATCTCT	ATGAAAATA	AAACAAAAA	TTAGCTGAAC	ATGGTGGTGT	18970
	GCGCCGTAG	TTCCAAACT	TGGGAGGCTG	AAGTGGGAGG	ATCCTTGAG	CCCAGGAGGT	GGAAAGTGA	19040
	GTGAGCTGAG	ATTGCACCA	TGTACTGCAG	CTGGGCTGAC	AGAGTGAAG	CCCATCTCAA	CAACAACAA	19110
	GAGAGCTGAC	AAATGCAGTT	TCTTGGAAAG	AAACATTTAG	TAGGAACCTA	ACCTACACAC	AGAAAGCCAG	19180
45	TCGGTGTCTC	GGTGTCACTG	AGATGAGATG	ATGGTCTCTC	ACACCATCAC	CCCAGACCCA	GGGTTTATGC	19250
	ACCACAGGGG	CGGGTGGCTC	AGAAGGGATG	CGCAGGACGT	TGATATACGA	TGACATCAAG	GTGTCTGAC	19320
	GAGGGGCGAG	ATTTCATGATA	AGTACTGCT	GGTACACAAG	GAACAATGGA	TAACTGGAA	ACCTTAGAGG	19390
	CCTTCCCGGA	ACAGGGGCTA	ATCAGAAGCC	AGCATGGGGG	GCTGGCATCC	AGGATGGAGC	TGCTTAGGCC	19460
	TCCACATGCG	TGTTCAATACA	GATGTTGCAC	AGAAACCGAG	TGTACTGTG	CACACACAGA	CACGAGCTA	19530
50	CTCGCACACA	CAAGCACACA	CACAGACATG	CATGCTGCA	TCCGTGTGTG	TGCACCTGTG	CCCATGAGGA	19600
	AACCCATGCA	TGTGCATTCA	TGCACGCACA	CAGGCACCGG	TGGGCCCATG	CCCACACCCA	CGAGCACCGT	19670
	CTGATTAGGA	GGCCTTTCT	CTGACGCTGT	CGGCATCCT	CTCAGGTTTC	ACGCATGTGT	GCTGACAGCT	19740
	CCATTCTATC	AGCAAGTTTG	GAAGAACCCC	ACATTTTTCC	TGCGGCTCAT	CTCTGACACG	GGGTTTATGC	19810
	GCTACTCCAT	CCTGAAGGCC	AAGAAGCCAG	GTATGTGCAG	GTGCTGGGCC	TCAGTGGCAG	CAGTGCCTGC	19880
55	CTGCTGGTGT	TAGTGTGTCA	GGAGACTGAG	TGAATCTGGG	CTTAGGAAGT	TCTTACCCCT	TTTCGCATCA	19950
	GGAAAGTGGT	TAACCCAACC	ACTGTCAGGC	TCGCTGTGCC	GCCTCTCGT	GGGGTGAACA	GAGCACCTGA	20020
	TGGAGGGGAC	AGGAGCTGTC	TGGGAGCTGC	CATCCTTCCC	ACCTTGTCT	GCCTGGGGAA	GCCTGGGGG	20090
	GCCTGGTCTC	TCTGTGTTGC	CCCATGGTGG	GATTTGGGGG	GCCTGGGCTC	TCTGTGTTGC	CCTGTGGTGG	20160
	GATTGGGCTG	TCTCCCGTCC	TGGGCACTTA	GGGCCCTTCT	GCAAAACCCAG	GCCAAGGGCT	TAGGAGGAGG	20230
60	CCAGGCCGAG	GCTACCCAC	CCCTCTCAGG	AGCAGAGGCC	GGGTATCAC	ACGACAGAGC	CCCGCCCGT	20300
	CCTCTGCTTC	CCAGTCAACG	TCTCTGCCC	CTGGACACTT	TGTCCAGCAT	CAGGGAGGTT	TCTGATCCGT	20370
	CTGAAATTC	AGCCATGTCG	AACCTGCGGT	CCTGAGCTTA	ACAGCTTCTA	CTTTCTGTTT	TTTCTGTGTT	20440
	GTGGAAATTT	CACCTGGAGA	AGCCGAAGAA	AACTTTCTG	TGCTGACTCC	TGCGGTGCTT	GGGTGGGAC	20510
	AGCCAGAGAT	SGAGCCACCC	CGCAGACCGT	CGGCTGTGGG	CAGCTTTCCG	GTGTCTCCCT	GGAGGGGAGC	20580
65	TGGGCTGGGC	CTGTGACTCC	TCAGCCTCTG	TTTTCCCCCA	GGGATGTCCG	TGGGGGCCAA	GGGCGCCGCG	20650
	GGCCCTCTGC	CCTCCGAGGC	CGTGCACTGG	CTGTGCCACC	AAGCATTCCT	GCTCAAGCTG	ACTCGACACC	20720
	GTGTCACTCA	CGTGCCACTC	CTGGGCTCAC	TCAGGACAGG	CAAGTGTCCG	TGGAGGCCAG	TGCGGGCCCC	20790
	ACTTGCCGAG	GGGTCACTCT	TGAACGCCCT	CTGTGGGGCG	AGCAGCTCA	GATGCTGCTG	AAGTGCAGAC	20860
	GGCCCGGGGC	CTGACCTTGG	GGGCTGGAG	CCACGCTGGC	AGCCCTATGT	GATTAAACGC	TGGTGTCCCC	20930
70	AGGCCACGGA	GCCTGGCAGG	GTCCCAACT	TCTTGAACCC	CTGCTTCCCA	TCTCAGGGGC	GATGGCTCCC	21000
	CACGCTTGGG	AGCCTTCTGA	CCCTGACCT	GTGTCTCTCT	ACAGCCTCTT	CCTTGGCTGC	TGCCCTGAGC	21070
	TCTTGGGGTC	CTGAGCAAGT	TCTCTCCCG	CCCCGCGGCT	CCAGCCTCAC	TGGGCTGCTC	TGCTGCTGCG	21140
	CCCGGTGGAG	GGGTCTCTGT	CCCTTCACTG	AGGTTCCAC	CAGCCAGGGC	CAGGAGGTGC	AGGCCCTGCC	21210
	TGCCCGGCCA	CCACACGCTC	CTAGAGGGT	TGGAGGATGG	CACCTCTGGT	CTCTTCTGGA	ACGGAGTCTG	21280
75	ATTTTGGGCC	CGCAGCCGAG	ACGCAGCTGA	GTCCGAAGCT	CCCGGGGAGC	AGCCTGACTG	CCCTGGAGGC	21350
	CGCAGCCGAG	CGGCACTGCT	CCTCAGACTT	CAAGACCAT	CTGGAGTGT	GGCCACCCGC	CCACAGCCAG	21420
	GGCAGAGCA	GACACACGCA	GGCCTGTAC	GGGCGGCTCT	AGTCCGAGG	GAGGGAGGGG	GGCCCCACAC	21490
	CCAGGCCCGC	ACCGCTGGGA	GTCTGAGGCC	TGAGTGAGTG	TTTGGCCGAG	CTCTGATGCT	CCGGCTGAAG	21560
	GCTGAGTGT	CGGCTGAGGC	CTGAGGGAGT	GTCCAGGCCA	GGGCTGAGTG	TCCAGGACAC	CTGCCCTCTT	21630

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	CACCTCCCCA	CAGGCTGGCG	CTCGGCTCCA	CCCCAGGGCC	AGCTTTTCTT	CACCAAGGAGC	CCGGCTTCCA	21700
	CTCCCCCAT	AGGAATAGTC	CATCCCCAGA	TTCGCCATTG	TTCACCCCTC	CCCCTGCCCT	CTTTTGCCTT	21770
	CCACCCCCAC	CATCCAGGTG	GAGACCCTGA	GAAGGACCCT	GGGAGCTCTG	GGAAATTGGA	GTGACCAAAG	21840
	GTGTGCCCTG	TACACAGGCG	AGGACCCTGC	ACCTGGATGG	GGGTCCCTGT	GGGTCAAATT	GGGGGGAGGT	21910
5	GCTGTGGGAG	TAAATACTG	AATATATGAG	TTTTTCAGTT	TTGAAAAAAA	TCTCATGTTT	GAATCCTAAT	21980
	GTGCACCTGA	TAGACACCCAC	TGTATGCAAT	TACAGAAGCC	TGTGAGTGAA	CGGGGTGGTG	GTCACTGCGG	22050
	GGCCATGGCC	TGGCTGTGCA	TTTACGGGAG	TCTATGAGTG	AATGGGGTTG	TGGTCAGTGC	GGGCCCCATG	22120
	CCTGGCTGGG	CCTGGGAGGT	TTCTGATGCT	GTGAGGCAGG	AGGGGAAGGA	GGGTAGGGGA	TAGACAGTGG	22190
	GAGCCCCCAC	CCTGGAAGAC	ATAACAGTAA	GTCCAGGCCC	GAAGGGCAGC	AGGGATGCTG	GGGGCCACGC	22260
10	TTGGGCGGCG	GGGATGATGG	AGGGCTGGCC	CAGGGTGCCA	GGGATGATGG	GGGCCCCAGC	TGGGGTGGCA	22330
	GGGGGTGATG	GGGGGGCTGG	TCTGGGTGGC	GGGGAAGATG	GGGAAGCCTG	GCTGGGCCCC	CTCCTCCCTT	22400
	GCCTCCACCC	TGCAGGCGTG	GATCCGGATG	TGCTTCCCTG	GTGCACATCC	TCTGGGCCAT	CAGCTTTCAT	22470
	GGAGGTGGGG	GGCAGGGGCA	TGACACCATC	CTGTATAAAA	TCCAGGATTC	CTCCTCCTGA	ACGCCCCAAAC	22540
	TCAGGTTGAA	AGTCACATTC	CGCCTCTGGC	CATTCTCTTA	AGAGTAGACC	AGGATTCTGA	TCTCTGAAGG	22610
15	GTGGGTAGGG	TGGGGCAGTG	GAGGGTGTGG	ACACAGGAGG	CTTCAGGGTG	GGGCTGGTGA	TGCTCTCTCA	22680
	TCCTCTTATC	ATCTCCCACT	CTCATCTCTC	ATCCTCTTAT	CATCTCCACG	TCTCATCTGT	CTTCCTCTTA	22750
	TCTCCCACTC	TCACTCTGCA	TCCTCTTACC	ATCTCCCACT	CTCATCTCTT	ATCCTCTTAT	CTCCTAGTCT	22820
	CATCCAGACT	TACCTCCCACT	AGCGGTGGCC	AGGCTCCGAG	TGGAGCTGGA	CATACGTCCT	TCCCTCAGGA	22890
20	GAAGGAACTG	GAAGGATTGC	AGAGAACAGG	AGCGGGCGCT	CAGAGGGAGC	CAGTCTTGGG	GTGAAGAAGC	22960
	AGCCCCCTCT	CAGAAGTTGG	CTTGGGCCAC	ACGAAACCGA	GGGCCCTGCG	TGAGTGGGTC	CAGAGCCTTC	23030
	CAGCAGGTCC	CTGGTGGGGC	CTTATGGTAT	GGCCGGGTCC	TACTGAGTGC	ACCTTGGACA	GGGCTTCTGG	23100
	TTTGAGTGCA	GGCCGGACGT	GCCTGGTGTG	GGGGTGGGGG	CTTATGGCCA	CTGGATATGG	CGTCATTTAT	23170
	TGCTGCTGCT	TCAGAGAATG	TCTGAGTGAC	CGAGCCTAAT	GTGTATGGTG	GGCCCAAGTC	CACAGACTGT	23240
	GTGCTAAATG	CAGTCTGGTG	CCTGGAGGCC	CCGTATAGGA	GCTGTGAGGA	AGGAGGGGCT	CTTGGCAGGC	23310
25	GGCCTGGGGG	CGCCTTTGCC	CTGCAAACTG	GAAGGSAGCG	GGCCCGGGCG	CCGTGGGGCG	ACGACCTCAA	23380
	GTGAGAGGTT	GGACAGAACA	GGCGGGGGAC	TTCCAGGAGG	CAGAGGGCCG	TGCTCAGGCA	CACCTGGGTT	23450
	TGAATCACAG	ACCAACGGGT	CAGGCCATTG	TTCACTATAT	CATCTTCTAC	AAAGCTCCAG	ATTCTGTGTT	23520
	CTCCGGGTGT	TTTTTTGTGA	AATTTTACTC	AGGATTACTT	ATATTTTTTG	CTAAAGTATT	AGACCCCTAA	23590
	AAAGGTTATT	TGCTTTGATA	TGGCTTAACT	CACTAAGCAC	CTACTTTATT	TGTCTGTTTT	TATTTATTAT	23660
30	TATTATTATT	ATTAGAGATG	GTGCTACTTC	TGTCACCCAG	GTGTTTAGTG	CAGTGGCACA	GTCACTGGCTC	23730
	GCTGTAGCCG	CAAAACCCCA	GGCTCAAGTG	ATCCTCCGGC	CTCAGCTTCC	CAGAGTGCTG	GGATTACAGG	23800
	TGTGAGCCAC	TGCCCTTGCC	TGGCACTTTT	AAAAACCACT	ATGTAAGGTC	AGGTCCAGTG	GCTTCCACAC	23870
	CTGTATCCCC	AGTAGTTTGG	GAAGCGGAGG	CAGAGGATTG	GTCTGAGGCC	AGGAGTTTGA	GACCAAGCATG	23940
35	GGTAACATAG	GGAGACCCCA	TCTCTACAAA	AAATGCAAAA	AGTTATCCGG	GCGTGGGGTC	CAGCATCTGT	24010
	AGTCCCAGCT	GCTCGGGAGG	CTGACTGSSA	GGATCGCTTG	AGCCCGGGAG	GTCTATGGCTG	CAGTGAAGCTG	24080
	TGATTGTACC	ATCGCACTCC	AGCCTGGGCA	ACAGAGTGAG	ACCCTGTCTC	AAAAAAAAAA	AAAAAAAAAG	24150
	AAGGAGAAGG	AGAAGAGAAG	AAGAAGGAAG	AAGGAAGAGG	AAGAAGGAAG	AAGAAGGAAG	AAGAAGGAAG	24220
	AAGGAGGCCT	GCTAGGTGCT	AGGTAGACTG	TCAATCTCA	GAGCAAAATG	AAATAAACAA	AGTTTAAAGG	24290
	GGAAAGAAAA	ACCCACAGTC	TTTGGACTTC	CTTAGGCCCTG	AACCTCATCT	CAAGCAGCTT	CCTTCCACAG	24360
40	ACAAGCCTGT	ATGGAGCGAG	TGAGTTCAAA	GCAGAAAGGG	AGGAGAAGCA	GGCAAGGGTG	GAGGCTGTGG	24430
	GTGACACAG	CCAGGACCCC	TGAAAGGGAG	TGGTTGTTTT	CCTGCCTCAG	CCCCACGCTC	CTGCCGGTCC	24500
	TGCACCTGCT	GTAACCGTGC	ATGTTGGTGC	CAGGTGCCCA	CCTGGGAAGG	ATGCTGTGCA	GGGGGCTTGC	24570
	CAAACTTTGG	TGGGTTTCAG	AAGCCCCAGG	CACCTGTGGC	AGGCACAATT	ACAGCCCTC	CCCAAGATG	24640
	CCCACGTCCT	TCTCCTGGAA	CCTGTGAATG	TGTCACCCGC	AAGGCAGAGG	CTGGTGAAGG	CTCCAGGTGG	24710
45	AATCACGGCT	GCCAGTCAGC	CGATCTTAAG	GTATCCTGG	ATTATCTGGT	GGGCTTGATA	TGGCCACAGG	24780
	GGTCCCTAGA	AGTGAGAGAG	GGAGGCAGGG	GAGAGTCAGA	GAGGGGACGT	GAGAAGGACC	ACTGGCCACT	24850
	GCTGGCTTTG	AGATGGAGGA	GGGGGTCCCC	AGCCAAGGAA	TGGGGGCAGC	CGCTCCATGC	TGGAAAAGCA	24920
	AGCAATGCTC	CCCGGTCCTG	AGGGCACAGG	GCCCTGCCCA	CGCCTCGATT	TCAGGCCAGT	GGGACCTGTT	24990
	TCAGCTTTCC	GGCCTCCAGA	GCTGTAAGAT	GATGCGTTTG	TGTTACGCCA	CTAAGCTGCA	GTGATTCCGT	25060
50	ACAGCAGCAA	ATGGAATAGC	AGTACAGGGA	AATGAATACA	GGGACAGTTC	TCAGAGTGAC	TCTCAGCCCA	25130
	CCCCCTGGG							25138

Example 5

- 55 Comparison of the above-described genomic hTC sequence and the sequence of the hTC cDNA (Fig. 6; corresponding to SEQ ID NO 2) made it possible to elucidate the exon-intron structure of the hTC gene. The genomic organization of the hTC gene is illustrated diagrammatically in Fig. 7. The coding region of the hTC gene is composed of 16 exons which vary in size between 62 bp and 1354 bp (see Table 1).
- 60 Exon 1 contains the translation start codon ATG. The translation stop codon TGA and the 3'-untranslated region lie on exon 16 (Fig. 8). No possible polyadenylation signal (AATAAA) was found either in exon 16 or in the 3195 bp of the following

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3'-flanking region. The exon-intron transitions were determined on the basis of the consensus sequence

	5'-Exon			Intron			3'-Exon		
5	Pre-mRNA	A/C	A G	G T	A/G	A	... N C	A G	G
	Frequency (%)	70	60 80	100 100	95	70	80 100	100 60	

and listed in Table 1. With the exception of the 5' splice site between exon 15 and
 10 intron 15, all the exon-intron transitions are in accord with the published (Shapiro
 and Senapathy, 1987) splice consensus sequence. The sizes of the introns are
 between 104 bp and 8616 bp. Since only part of intron 6 was isolated, it is not
 possible to determine the precise length of the hTC gene. Based on the part sequence
 of ~4660 bp, which was obtained from intron 6, the minimum size of the hTERT
 gene is 37 kb.

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Introns 1-5 and the 5' region of intron 6, are contained in contig 1:

Intron 1: bp 11493-11596 (SEQ ID NO 4);

Intron 2: bp 12951-21566 (SEQ ID NO 5);

Intron 3: bp 21763-23851 (SEQ ID NO 6);

5 Intron 4: bp 24033-24719 (SEQ ID NO 7);

Intron 5: bp 24900-25393 (SEQ ID NO 8);

5' region of intron 6: bp 25550-26414 (SEQ ID NO 9).

10 The 3' region of intron 6, and introns 7-15, are located in contig 2 at the following positions:

3' region of intron 6: bp 1-3782 (SEQ ID NO 10);

Intron 7: bp 3879-4858 (SEQ ID NO 11);

Intron 8: bp 4945-7429 (SEQ ID NO 12);

Intron 9: bp 7544-9527 (SEQ ID NO 13);

15 Intron 10: bp 9600-11470 (SEQ ID NO 14);

Intron 11: bp 11660-15460 (SEQ ID NO 15);

Intron 12: bp 15588-16467 (SEQ ID NO 16);

Intron 13: bp 16530-19715 (SEQ ID NO 17);

Intron 14: 19841-20621 (SEQ ID NO 18);

20 Intron 15: 20760-21295 (SEQ ID NO 19).

The 3'-untranscribed region is also located in contig 2 at position 21960-25138 (SEQ ID NO 20).

25 The individual sequences of the abovementioned introns are as follows:

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Intron 1 (SEQ ID NO 4)

GTGGGCTCCCGGGGTGGCGTCCGGCTGGGGTTGAGGGCGGCCGGGGGAACCAGCGACATGCGGAGAGCAGCGCAGG
CGACTCAGGGCGCTTCCCCCGCAG

5 **Intron 2 (SEQ ID NO 5)**

GTGAGGAGGTGGTGGCCGTGAGAGGCCAGGCCAGAGCTGAATGCAGTAGGGGCTCAGAAAAGGGGGCAGGCAGAGCC
CTGGTCCTCCTGTCTCCATCGTCACGTGGGCACACGTGGCTTTTCGCTCAGGACGTGAGTGGACACGGTGATCTCTGCC
TCTGCTCTCCCTCCTGTCCAGTTTGCATAAACTTACGAGGTTACCTTCACGTTTTGATGGACACGCGGTTCCAGGCGC
CGAGGCCAGAGCAGTGAACAGAGGAGGCTGGGCGCGGAGTGGAGCCGGGTTGCCGCAATGGGGAGAAGTGTCTGGAAG
10 CACAGACGCTCTGGCGAGGGTGCTGACAGTTACCTATAATCCTCTTCGCAATTTCAAGGGTGGGAATGAGAGGTGGGGA
CGAGAACCCCTCTTCTGGGGTGGGAGGTAAGGGTTTTGCAGGTGCACGTGGTCAGCCAATATGAGGTTTGTGTTTA
AGATTTAATTGTGTGTGACGGCCAGGTGCGGTGGCTACGCCGGTAATCCAGCACCTTTGGGAAGCTGAGGCAGGTGGA
TCACCTGAGGTGAGGAGTTTGAACAGCCTGACCAACATGGTGAACCCCTATCTGTACTAAAAATACAAAAATTAGCTG
GGCATGGTGGTGTGCTGTAATCCAGCTACTTGGGAGGCTGAGGCAGGAGAATCACTTGAACCCAGGAGGCGGAGGC
15 TGCAGTGAGCTGAGATTGTGCCATTGTACTCCAGCCTGGGCGACAAGAGTGAACCTGTCTTTAAAAAAGTGT
CGTTGATTGTGCCAGGACAGGGTAGAGGGAGGAGATAAGACTGTTCTCCAGCACAGATCCTGGTCCCATCTTTAGGTAT
GAAGAGGGCCACATGGGAGCAGAGGACAGCAGATGGCTCCACCTGCTGAGGAAGGGACAGTGTGTGGGTTTCAGGGG
ATGGTGTCTGCTGGGCCCTGCCGTGTCCCCACCCTGTTTTCTGGATTGTATGTTGAGGAACCTCCGCTCCAGCCCCCTT
TGGCTCCAGTGCTCCAGGCCCTACCGTGGCAGCTAGAAGAAGTCCCGATTTCACCCCTCCCAACACTCCCAAGAC
20 ATGTAAGACTTCCGGCCATGCAGACAAGGAGGGTGACCTTCTTGGGGCTCTTTTTTCTTTTTTCTTTTATGGTGGC
AAAAGTCATATAACATGAGATTGGCACTCCTAACACCGTTTTCTGTGTACAGTGCAGAATTGCTAACTCGGCGGTGTTTA
CAGCAGGTTGCTTGAATGCTGCGTCTTGGCTGACTGGAAGTCCCTACCCATCGAACGGCAGCTGCCCTCACACCTGCTGC
GGCTCAGGTGGACACGCCGAGTCAGATAAGCGTCATGCAACCCAGTTTTGCTTTTTGTGCTCCAGCTTCTTCTGTTAG
GAGAGTTTGAGTTCTCTGATCAGGACTCTGCCTGTCTATGCTGTTCTCTGACTTCAGATGAGGTACAAATCTGCCCCCTGG
25 CTTATGCAGGGAGTGAAGCGTGGTCCCCGGGTGTCCTGTACAGTGCAGGGTGAGTGAGGCGTTGCCCCAGGTGTCCCT
GTCACGTGTAGGGTGAGTGAGGCGCGGCCCGGGTGTCCCTGTCCCGTGCAGCGTGATTGAGGTGTGGCCCCCGGGTGT
CCCTGTACAGTGTAGGGTGAGTGAGGCGCCATCCCCGGGTGTCCCTGTACAGTGTAGGGTGAGTGAGGCGTGGTCCCCGG
GTGTCCTGTCCCGTGCAGGGTGAGTGAGGCACTGTCCCCGGGTGTCCCTGTACAGTGCAGGGTGAGTGAGGCGCGGTCC
CCGGGTGTCCCTCTCAGGTGTAGGGTGAGTGAGGCGCGGCCCGGGTGTCCCTGTACAGTGTAGGGTGAGTGAGGCAAC
30 GTCCCTGGGTGTCCCTCCAGGTATAGGGTGAGTGAGGCACTGTCCCCGGGTGTCCCTGTACAGTGCAGGGTGAGTGAGG
CGCGGCCCGGGGTGTCCCTCTCAGGTGCAGGGTGAGTGAGGCGCTGTCCCTGGGTGTCCCTGTCTGTTAGGGTGAGT
GAGGCTCTGTCCCGAGGTGCTTGGCGTTTGTCTACTTGAGCTTGCTCCTGAATGTTTGCTCTTTCTATAGCCACAGCT
GCGCCGGTTGCCATTGCTGGGTAGATGCTGAGGCGCAGTGTGGTCCCCAAGCCTATCTTTCTGATGCTCGGCTCT
TCTTGGTCACCTCTCCGTTCCATTTTGCTACGGGGACACGGGACTGCAGGCTCTCGCCTCCGCGTGCCAGGCACTGCAG
35 CCACAGCTTCAGGTCCGCTTGCTCTGTGGGCTGGCTGTCTCAGCAGTGGCCGCCACATGCATGCTGCCAATACTCC
TCTCCAGCTTGTCTCATGCCGAGGCTGGACTCTGGGCTGCTGTCTGTCTGCCAGTGTGCTGGAGACATCCAGAA
AGGGTTCTGTGTCCTGAAGGAAAGCAAGTCAACCCAGCCCCCTCACTTGCTCTGTTTTCTCCCAAGCTGCCCTCTGC
TTGGCCCCCTTGGGTGGGTGGCAACGCTTGTACCTTATTCTGGGCACCTGCCGCTCATTTGCTTAGGCTGGGCTGTGCT
CCAGTCCGCCCCCTCACATGGATTGACGTCCAGGCACAGGTTGGAGTGTCTGTCTGTCTCTGCTCTGAGACCCAGCTG
40 GAGGGCCGGTGTCTCCGCCAGCCTTCGTGAGACTTCCCTCTGGGTCTTAGTTTTGAATTTCACTGATTTACCTCTGACG
TTTTCTATCTCTCCATTGTATGCTTTTTCTTGGTTTATTCTTTTCACTTCTTAGTTTAGTCTATGCCTTTC
CCTCTAAGTGTGCTTACCTGCACCTGTGTTTTGATGTGAAGTAATCTCAACATCAGCCACTTTCAAGTGTCTTAAA
ATACTTCAAAGTGTTAATACTTCTTTAAGTATTCTTATTCTGTGATTTTTTCTTTGTGCACGCTGTGTTTTGACGTGA
AATCATTTTGATATCAGTGACTTTTAAGTATTCTTACGTTATTCTGTGATTCTTTGAGCAGTGAGTTATTGAACACT
45 GTTTATGTTCAAGATATGTAGAGTATCAAGATACCTAGAGTATTTAAGTTATCATTTTATTATTGATTTCTAACTCAGT
TGTGTAGTGGTCTGTATAATAACCAATTATTTGAAGTTTGGGAGCCTTGCTTTGTGATCTAGTGTGTCATGGTTCCAG
AACTGTCCATTGTAAATTTGACATCCTGTCAATAGTGGCATGCATGTTCACTATATCCAGCTTATTAAGGTCCAGTGCA

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AAGCTTCTGTCTCCTTCTAGATGCATGAAATTC AAGAAGGAGGCCATAGTCCCTCACCTGGGGGATGGGTCTGTTCAATT
 TCTTCTCGTTTGGTAGCATTTATGTGAGGCATTGTTAGGTGCATGCACGTGGTAGAATTTTTATCTTCTGATGAGTGAA
 TCTTTTGGAGACTTCTATGTCTCTAGTAATCTAGTAATTTCTTTTAAATTGCTCTTAGTACTGCCACACTGGGCTTCT
 TTTGATTAGTATTTTCTGCTGTGCTGTTTCTGCCTTTAATTTATATATATATATATATTTTTTTTTTTTGAGACA
 5 GAGTCTTGGTCTGTGCGCCAGGGTGAGTGCAGTGGTGTGATCACAGSTCAGTGAACTTTACCTTCTGGCCTGAGCCGT
 CCTCTCACCTCAGCCTCCTGAGTAGCTGGAACGACAGACGCGCTACACCTGGCTAATTTTAAATTTTTCTGGA
 GACAGGGTCTTGCTGTGTTGCCAGGCTGGTCTCAAACCTTTGGACTCAAGGGATCCATCTACCTCGGCTTCCCAAAGTG
 CTGAATTACAGGCATGAGCCACCATGTCTGGCCTAATTTTCAACACTTTTATATTCTTATAGTGTGGGTATGCTCTGTTA
 ACAGCATGTAGGTGAATTTCCAATCCAGTCTGACAGTCTGTTTAACTGGATAACCTGATTTATTTTCATTTTTTGTGTC
 10 ACTAGAGACCCGCTGGTGCACCTCTGATTCTCCACTTGCCTGTTGCATGTCCTCGTCCCTGTTTCTCACCACCTCTTG
 GGTGGCATGTGCGTTTCTGCGGAGTGTGTGTTGATCCTCTCGTGGCTCCTGGTCACTGGGCATTTGCTTTTATTTCT
 CTTTGCTTAGTGTACCCCTGATCTTTTTATTGTGCTGTTGCTTTTGTGTTATTGAGACAGTCTCACTCTGTCACCCA
 GGCTGGAGTGTAAATGGCACAATCTCGGCTCACTGCAACCTCTGCTCCTCGGTTCAAGCAGTTCTCATTCCTCAACCTCA
 TGAGTAGCTGGGATTACAGGCGCCACCACCGCTGGCTAATTTTGTATTTTAGTAGAGATAGGCTTTACCATGT
 15 TGGCCAGGCTGGTCTCAAACCTGACCTCAAGTGTCTGCGCCGCTTGGCCTCCACAGTGTGGGATTACAGGTGCAA
 GCCACCGTGCCCGGATACCTTGATCTTTTAAATGAAGTCTGAAACATTGCTACCCCTGTCTGAGCAATAAGACCCCTT
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 CCCCCACAAGCTAAGCATTTATTAATATTGTTTCCGTGTTGAGTGTCTGTAGCTTTGCCCCCGCCCTGCTTTCTCTCC
 TTTGTTCCCCGTCTGTCTTCTGTCTCAGGCCCGCCGTCTGGGGTCCCCCTCCTTGTCTCTTGGTGGTCTTCTGTCTTG
 20 TTATTGCTGGTAAACCCAGCTTTACCTGTGCTGGCCTCCATGGCATCTAGCGAGCTCCGGGACCTCTGCTTATGATGC
 ACAGATGAAGATGTGGAGACTCACGAGGAGGGCGGTCTCTTGGCCCGTGAAGTGTCTGGAGCACCACGTGGCCAGCGTTC
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 CCGCGGTGTGAGTTTGAATCGCGCAACCTGCGGTGTGGCGCCAGCTCTGACGGTGTGCTGCGCCACAGGAGCATGACGTGAGCC
 CTTCTCCCTTCTGCTTGGGAACAGGACAAAGGATGAGGCTCCGAGCCGTTGTGCCCCAACAGGAGCATGACGTGAGCC
 25 ATGTGGATAATTTTAAATTTCTAGGCTGGGCGCGGTGGCTCACGCCCTGAATCCAGCACTTTGGGAGGCCAAGGCGGG
 TGGATCACGAGGTGAGGAGGTGAGACCATCCTGGCCACATGATGAAACCCATCTGTAATAAAACACAAAATTAGC
 TGGGCGTGGTGGCGGTGCTGTAATCCAGCTACTCGGGAGGCTGAGGCAGGAGAATTGCTTGAACCTGGGAGTTGGAA
 GTTGAGTGAGCCGACATTGCACCACTGCACTCCAGCCTGGCAACACAGCGAGACTCTGTCTCAAAAAAAAAAAAAAAA
 AAAAAAAAAAATTCTAGTAGCCACATTAAAAAGTAAAAAGAAAAGGTGAAATTAATGTAATAATAGATTTTACTGAA
 30 GCCCAGCATGTCCACACCTCATATTTAGGGTGTATTGTTGGGAGCATCACTCACAGGACATTTGACATTTTTTGAGC
 TTTGTCTGCGGGATCCCGTGTGTAGGTCCCGTGCCTGGCCATCTCGGCTGGACCTGCTGGGCTTCCCATGGCCATGGCT
 GTTGATACAGATGGTGCAGSTCCGGGATGAGGTGCGCCAGGCCCTCAGTGAGCTGGATGTGAGTGTCCGGATGGTGCAGC
 TCTGGGATGAGGTGCGCCAGGCCCTGCTGTGAGCTGGATGTGTGGTGTCTGGATGGTGCAGGTGAGGGTGAGGTCTCCAG
 GCCCTCGGTGAGCTGGAGGTATGGAGTCCGGATGATGCAGGTCCGGGTGAGGTGCGCCAGGCCCTGCTGTGAGCTGGATG
 35 TGTGGTGTCTGGATGGTGCAGGTGAGGGTGAGGTCTCCAGGCCCTCGGTAAGCTGGAGGTATGGAGTCCGGATGATGCA
 GGTCCGGGGTGAGGTGCGCCAGGCCCTGCTGTGAGCTGGATGTGTGGTGTCTGGATGGTGCAGGTCTGGGGTGAGGTGACC
 AGGCCCTGCGGTGAGCTGGGTGTGCGGTGTCTGGATGGTGCAGGTCTGGAGTGAGGTGCGCCAGACGGTGCCAGACCATGC
 GGTGAGCTGGATATGCGGTGTCCGGATGGTGCAGGTCTGGGGTGAGGTGCGCCAGGCCCTGCTGTGAGTTGGATGTGGGGT
 GTCCGGATGTGAGGTCCGGTGTGAGGTGAGGAGGCCCTGCTGTGAGCTGGATGTGTGGTGTCTGGATGGTGCAGGTCT
 40 GGGGTGAAGGTGCGCCAGGCCCTGCTGTGAGCTGGATGTGTGGTGTCTGGATGGTGCAGGTCTGGAGTGAGGTGCGCCAG
 GCCCTCGGTGAGCTGGATGTGAGGTGCTCAGATGTGAGGTGCGGGGTGAGGTGCGCCAGACCCCTGCGGTGAGCTGGATG
 TGCGGTGTCTGGATGTGAGGTCTGGAGTGAGGTGCGCCAGGCCCTCGGTGAGCTGGATGTATGGAGTCCGGATGGTGCC
 GGTCCGGGGTGAGGTGCGCCAGACCCCTGCTGTGAGCTGGATGTGCGGTGTCTGGATGGTACAGGTCTGGAGTGAGGTGCGC
 AGACCCCTGCTGTGAGCTGGATATGCGGTGTCCGGATGGTGCAGGTGAGGGTGAGGTCTCCAGGCCCTCGGTGAGCTGGA
 45 GGTATGAGGTCCGGATGATGCAGGTGCGGGGTGAGGTGCGCCAGGCCCTGCTGTGAACCTGGATGTGCGGGCTGTGGATGGT
 GCAGGTCTGGGTGTGGTCCCGAGGCCCTCGGTGAGCTGGAGGTATGGAGTCCGGATGATGCAGGTCCGGGGTGAGGTGCG
 CCAGGCCCTGCTGTGAGCTGGATGTGCGGGCTCTGGATGGTGCAGGTCTGGGGTGAGGTGCGCCAGGCCCTCGGTGAGCTG

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GAGGTATGGAGTCCGGATGATGCAGGTCCGGGGTGAGSTTCCAGGCCCTGCTGTGAGCTGGATGTGCTGTATCCGGATG
 GTGCAGTCCGGGGTGAGGTCCAGGCCCTGCTGTGAGCTGGATGTGCTGTATCCGGATGGTGCAGGTCTGGGGTGAGST
 CACCAGGCCCTGCGGTGAGCTGGTTGTGCGGTGTCCGGTTGCTGCAGGTCCGGGGTGAGTTCCGAGGCCCTCGGTGAGC
 TGGATGTGCGGTGTCCCGTGTCCGGATGGTGCAGGTCCAGGGTGAGGTGCTAGGCCCTTGGTGGGCTGGATGTCCGT
 5 GTCCGGATGGTGCAGGTCTGGGGTGAGGTCCAGGCCCTTGGTGAGCTGGATGTGCGGTGTCTGCATGGTGCAGGTCTG
 GGGTGAGGTCCAGGCCCTTGGTGGGCTGGATGTGTTGGTGTCCGGATGGTGCAGGTCCGGCGTGAGGTCCAGGCCCT
 GCTGTGAGCTGGATGTGCGGTGTCTGGATGGTGCAGGTCCGGGGTGAGGTAGCCAAGGCCCTTCGGTGAGCTGGATGTGGG
 GTGTCCGGATGGTGCAGGTCCGGGGTGAGGTCCAGGCCCTGCGGTTAGCTGGATATGCGGTGTCCGGATGGTGCAGGT
 CCGGGGTGAGGTCAACAGGCCCTGCGGTTAGCTGGATGTGCGGTGTCTGGATGGTGCAGGTCCGGGGTGAGGTCCAGG
 10 CCTGCTGTGAGCTGGATGTGCTGTATCCGGATGGTGCAGGTCCGGGGTGAGGTCCAGGCCCTGCAGTGAGCTGGATG
 TGCTGTATCCGGATGGTGCAGGTCTGGCGTGAGGTCCAGGCCCTGCGGTTAGCTGGATATGCGGTGTCCGGATGGTGC
 GGTCCGGGGTGAGGTCAACAGGCCCTGCGGTTAGCTGGATGTGCGGTGTCCGGATGGTGCAGGTCTGGGGTGAGGTCCG
 AGGCCCTGCTGTGAGCTGGATGTGCTGTATCCGGATGGTGCAGGTCCGGGGTGAGGTCCAGGCCCTGCGGTGAGCTGG
 ATGTGCTGTATCCGGATGGTGCAGGTCTGGCGTGAGGTCCAGGCCCTGCGGTGAGCTGGATGTGAGTGTACGGATGG
 15 TGCAGGTCCGGGGTGAGGTCCAGGCCCTGCGGTGGGCTGTATGTGTGTCTGGATGGTGCAGGTCCGGGGTGAGTT
 CGCCAGGCCCTGCGGTGAGCTGGATGTGTGGTGTCTGGATGTGAGGTCCGGGGTGAGTTCCAGGCCCTCGGTGAGC
 TGGATATGCGGTGTCCCGTGTCCGAATGGTGCAGGTCCAGGGTGAGGTCCAGGCCCTTGGTGGGCTGGATGTCCGT
 GTCCGGATGGTGCAGGTCTGGGGTGAGGTCCAGGCCCTTGGTGAGCTGGATGTGCGGTGTCCGGATGGTGCAGGTCCG
 GGGTGAGGTCAACAGGCCCTGCGGTGATCTGGATGTGGCATGTCTCTCGTTAAG

20

Intron 3 (SEQ ID NO 6)

GTACTGTATCCCCAGGCCAGGCCCTGTGCTTCTCGAAGTCTTGAACACCAGGCCCGCCCTCAGCATGCGCCTGTCTCCACT
 TGCCCTGTGCTTCCCTGGCTGTGCAGCTCTGGGCTGGGAGCCAGGGGCCCGCTCACAGGCCCTGGTCCAAGTGGATTCTGTG
 CAAGGCTCTGACTGCCTGGAGCTCACGTTCTCTTACTTGTAAATCAGGAGTTTGTGCCAAGTGGTCTCTAGGGTTTGT
 25 AAGCAGAAGGGATTTAAATTAGATGAAACACTACCACTAGCCCTCCTTGCCCTTCCCTGGGATGTGGGTCTGATTCTCTC
 TCTCTTTTTTTTTCTTTTTGAGATGGAGTCTCACTCTGTTGCCAGGCTGGAGTGCAGTGGCATAATCTTGGCTCACT
 GCAACCTCCACCTCCTGGGTTAAGCGATTCAACAGCCTCAGCCCTCTAAGTAGCTGGGATTACAGGCACCTGCCACCAC
 GCGTGGCTAATTTTTGTACTTTTAGGAGAGACGGGGTTTACCATGTTGGCCAGGCTGGTCTCGAACTCATGACCTCAGG
 TGATCCACCCACCTTGGCCTCCCAAGTGTGGGTTTACAGGCTAAGCCACCGTCCAGCCCCGATTTCTTTTAAATT
 30 CATGCTGTTCTGTATGAATCTTCAATCTATTGSATTTAGGTGATGAGAGGATAAAATCCACCCACTTGGCGACTCACTG
 CAGGGAGCACCTGTGCAGGGAGCACCTGGGGATAGGAGAGTTCCACCATGAGCTAACTTCTAGGTGGCTGCATTTGAATG
 GCTGTGAGATTTGTCTGCAATGTTCCGGCTGATGAGAGTGTGAGATTGTGACAGATTCAAGCTGGATTGTCATCAGTGAG
 GGACGGGAGCGCTGGTCTGGGAGATGCCAGCCTGGCTGAGCCAGGCCATGGTATTAGCTTCTCCGTGTCCCGCCAGGC
 TGACTGTGGAGGGCTTTAGTCAGAAGATCAGGGCTTCCCAGCTCCCTGCACACTCGAGTCCCTGGGGGGCCTTGTGAC
 35 ACCCATGCCCCAAATCAGGATGTCTGCAGAGGGAGCTGGCAGCAGACCTCGTCAGAGGTAACACAGCCTCTGGGCTGGG
 GACCCCGACCTGGTGTGGGGCCATTTCCTTGCACTCTGGGGAGGGTCAGGGCTTCCCTGTGGGAACAAGTTAATACAC
 AATGCACCTTACTTAGACTTTACACGTATTTAATGGTGTGCGACCAACATGGTCAATTGACAGTATTTGGAAAGAAT
 TTAATTGGGGTGACCGGAAGGAGCAGACAGACSTGGTGGTCCCCAAGATGCTCCTTGTCACTACTGGGACTGTTGTTCTG
 CCTGGGGGGCCTTGGAGGCCCTCCTCCCTGGACAGGGTACCGTGCCCTTTCTACTCTGCTGGGCTGCGGCCTGCGGTG
 40 AGGGCACAGCTCCGGAGCACCGCGGCCCCAGTGTCCACGGAGTGCCAGGCTGTGAGCCACAGATGCCAGGTCCAGGT
 GTGGCCGCTCCAGCCCCCGTGCCCCATGGGTGGTTTGGGGGAAAGGCCAAGGGCAGAGGTGTGAGGAGACTGGTGGG
 CTCATGAGAGCTGATTTGCTCCTTGGCTGAGCTGCCCTGAGCAGCCTCTCCCGCCTCTCCATCTGAAGGGATGTGGCT
 CTTTCTACCTGGGGTCTGCTGGGGCCAGCTTGGGCTACCCAGTGGCTGTACAGAGGGACAGGCATCCTGTGTGG
 AGGGGATGGGTTACGTGGCCCCAGATGCAGCCTGGGACAGGCTCCCTGGTGTGATGGTGGGACAGTCAACCTGGGG
 45 GTTGACCGCCGACTGGGCTGCCAGGGTTGACTATAGGACCAGGTGTCCAGGTGCCCTGCAAGTAGAGGGGCTCTCAG
 AGGCGCTGGCTGGCATGGGTGGACGTGGCCCCGGGCATGGCCTTCAGCGTGTGCTGCCGTGGGTGCCCTGAGCCCTCAC
 TGAGTCGGTGGGGCTTGTGGCTTCCCGTGAAGTCTCCCGCTAGTCTGTTGTCTGGCTGAGCAAGCCTCTGAGGGGCTCT
 CTATTGCAG

Intron 5 (SEQ ID NO 8)

20

5'-region intron 6 (SEQ ID NO 9)

25

3'-region intron 6 (SEQ ID NO 10)

35 TGTGGGATTGGT¹TTTCATGTGTGGGATAGGTGGGGATCTGTGGGATTGGT²TTTATGAGTGGGGTAAACACAGAGTTCAAG
GGGAGCTTTCTCTCTGTAGTGGGTCTGCAGGTGCTCCAACAGCTTTATTGAGGAGACCATATCTTCTTTGAACTATGGT
C3GGGT³TATAGTAAGTCAGGGGTGTGGAGGCTCCCTGGGCTCCCTGTTCTGTTTCTTCCACTCTG3GGTGGTGTGGT
CTGCTGTGGTGTGTGGCGGTGGGCAGGGCTTCCAGGCTCCTTGTGTTTCATTGGCTGGATGTG⁴CCCTGGCTACGGT
CGGTCTTGGAA⁵TCCCTGCGAGTGGAGGCTTCTTTCTTTCTTTTCTTTCTTTT⁶TTTTTTTTTGGATAACAGA
40 GTCTCGCTCTTTTTTGGCAGGCTGGAGTGGTTTGGCGTGATCTTGGCTCACTGCAACCTGTGCTTCTGACTTCAAGCA
ATTCTCTTGCCTCAGCTCCCAAGTAGCTGGAATTATAGCGGCCACCACCATGCTGACTAATTTTCTAATTTTAGTAG
AGACGAGGT⁷TTCTCCATGTTGGCCAGGCTGGTCTCGAACTCCTGACCTCAGGTGATCTTCCACCTGGGCTCCCAAAGT
G⁸TGGGATGACAGGTGTGAACSCCGCGCCCGGCCGAGACTCGCTTCTGCAGCTTCGGTGGATCT⁹CCAGGATAGCTG
CTGCAGCCTTGGTGTGACAACCTCCGTTTCTCTCTCAGGTCTCGCTAGGGGTCTTTCTATTATGATCTCTCTTCA

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CAGAAGAGTTTCACGTGTGCTGATTTCCTGGCTGTTTCTGCGTAATTGGTGTCTGCTGTTTATCGATGGCCTCCTTCCA
 TTTCCTTTAGGCTTTGTTTATTGTTGTTTTTCCGGCTCCTTGAAGGAAAAGTTTCGATTATGGATGTTTGAACCTTCTTT
 TCTAAACAAGCATCTGAAGTTGCCGTTTTCCCTCTAAAGCAGGGATCCCAGGCCCTGGCTGTGGAGTGGCACCGGTCT
 5 GGGGCTGTAGGAACCCGGCGCACAGCGGAGGCTAGGTGGGTGTGGGAGCCAGCGTTCCCGCTGAGCCCCGCCCC
 TCTCAGATCAGCAGTGGCATGCGGTGCTCAGAGGCGCACACCCCTACTGAGAACTGTGCGTGAGAGGGGTCTAGATTCT
 GTGCTCCTTATGGGAATCTAATGCCTGATGATCTGAGGTGGAACCGTTTGCTCCCAAACCATCCCTTCCCACTGCTG
 TCCTGTGGAATAATCGTCTTCCACGAAACAGTCCCTGGTACCACAATGGTGGGGACCTGTGCTAAAGACCTGCTTCA
 GCAGCCTCTCGTCAGTGTGATATATTGGCTTTTCTGTGTGAGTCCAGAATAATTACGGATTTCTGTGATGCTTCCGC
 CGACCTCAGACCATGGGCTATTTGTGGGCGTGTGCTGCTCCTGGGTGGGAAGGGTGACGGCCCATGTACCTTCTCT
 10 GTTACTGCCTTCCAGTTGGTTCTCAGGGTTGAATCGTACTCGATGTGGTTTTAGCCACGGCCCTGCCGCCAGCTCCTG
 GGGGCTGGGAACATGCTGAAGCACAGASTCACCGTGCCTCTTTGATGCCTCACAAGCTCGAGGCTCCTGTGTCCG
 TGTTAGTGTGTGTCACGTGCCTGCTCACATCTGTCTTGGGACGCAGGGGCTTAGCAGGTCCCGTAGTAATGACAAGC
 GTCTGGGGAGTCTGCAGAAAGGAGGTGGGGTGCCGGTCTCTCTCCCGCTCTTCACTCTTCTCTGCTGTGCT
 GTGGCTGCACCTGCATCCCTGCAATCCCTCCAGCACTGGGCTGGAGAGGCCGGGAGCTCGAGTGCACCTTGTGCCACGT
 15 GACTGTGGATGGCAGTCGGTCACGGGGGTCTGATGTGTGGTGACTGTGGATGGCGGTGGTGCACAGGGGTCTGATGTGTG
 GTGACTGTGGATGGCGGTCTGAGTGTGGTGACTGTGGATGGCGGTCTGAGTGTGTGGTGACTGTGGATGGCGGTCTGATG
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 GGGTCTGATGTGGTGACTGTGGATGGCAGTCGTGGGTCTGATGTGTGGTGACTGTGGATGGCGGTCTGAGTGTGTGGTG
 TGGTGACTGTGGATGGCAGTCGTGGGTCTGATGTGTGGTGACTGTGGATGGCGGTCTGAGTGTGTGGTGACTGTGGATGG
 20 GTGGATGGCGGTCTGAGTGTGTGGTGACTGTGGATGGCGGTCTGAGTGTGTGGTGACTGTGGATGGCGGTCTGAGTGTGTGGTG
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 25 GATGTGTGGTGACTGTGGATGGCGGTCTGAGTGTGTGGTGACTGTGGATGGCGGTCTGAGTGTGTGGTGACTGTGGATGGCGGT
 GACTGTGGATGGCGGTCTGAGTGTGTGGTGACTGTGGATGGCGGTCTGAGTGTGTGGTGACTGTGGATGGCGGTCTGAGTGTGTGGTG
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 GCGGTCTGAGTGTGGTGACTGTGGATGGCGGTCTGAGTGTGTGGTGACTGTGGATGGCGGTCTGAGTGTGTGGTG
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 30 GGTGACTGTGGATGGCGGTCTGAGTGTGTGGTGACTGTGGATGGCGGTCTGAGTGTGTGGTGACTGTGGATGGCGGTCTGAGTGTGTGGTG
 GACTGTGGATGGCGGTCTGAGTGTGTGGTGACTGTGGATGGCGGTCTGAGTGTGTGGTGACTGTGGATGGCGGTCTGAGTGTGTGGTG
 GCGGTCTGAGTGTGGTGACTGTGGATGGCGGTCTGAGTGTGTGGTGACTGTGGATGGCGGTCTGAGTGTGTGGTG
 GCGGTCTGAGTGTGGTGACTGTGGATGGCGGTCTGAGTGTGTGGTGACTGTGGATGGCGGTCTGAGTGTGTGGTG
 GTGAGGGGTCTGAGTGTGTGGTGACTGTGGATGGCGGTCTGAGTGTGTGGTGACTGTGGATGGCGGTCTGAGTGTGTGGTG
 35 GGTCTGATGTGTGGTGACTGTGGATGGCGGTCTGAGTGTGTGGTGACTGTGGATGGCGGTCTGAGTGTGTGGTG
 GTGGTGACTGTGGATGGCGGTCTGAGTGTGTGGTGACTGTGGATGGCGGTCTGAGTGTGTGGTGACTGTGGATGGCGGTCTGAGTGTGTGGTG
 ACTTTGCGTCTCGGCCCGGCCCGGTTTTCCAAACAGAAGCTTCCAGGCGCTCTCTGGGCTTCATCCGCCATCG
 GGCTTGGCCGAGGTCCACACGTCCTGATCGGAAGAAACAAGTGCCAGCTCTGGCCGGGACAGGCACATTGTGGGCTC
 ATGCCCTCTCCTCTGCCGGCAG

40 **Intron 7 (SEQ ID NO 11)**

GTCTGGGCACTGCCCTGCAGGGTTGGGCAAGGACTCCAGCAGTGGGTCTCCCTGGGCAATCAATGGGCTCATGACG
 GACAGACTCTTGGCCCTGGGGGAGTGGGGGAATGAGCTGTGATGGGGCATGATGAGCTGTGTGCTTGGCGAAATC
 TGACCTGGGCAATGCCAGCTGGGACAGCTGCTGCATTACGGCACCTGCTCAGCTTGAAGTGGCGGCTCTCTCAAT
 CCGCAGTGCTTGTTCATGATTTGCTAAATGCTTCTCTGCCAGTTTGTGATCTTGAAGCCAAAGGAAAGGTGTCCCT
 45 CCTTTAGGAGGGCAGGCATGTTTGAAGCGTGTCTGCCAGCTGGCCCTCAGTGTGTGGTCTGAGGCCAAAGGAAACG
 TGCCCCCTCTTAGGAGGACGGGCGTGTGAGGCAGGCCCGCTGAGCGGGCTCTCAGTGTGGTGTGTGCAAT

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5 GGCCTGTGGCCCTTTGCAGATGTGGTCTGTCCACGTGGCCCTGTGGCTCTTTGCAGATGCCTGTAGCACTTGCTCGGC
TCTAGGGGACAGTCGTGTCCACCGCATGAGGCTCAGAGACCTCTGGGCGAATTTCTTGGCTCCCAGGGTGGGGGTGGAG
GTGGCTGGGCTGTGGGACCCAGACCTGTGCCCGGCAGCTGGGAGCAACTCTGGATCACATATGCCATCCGGGCCA
CGGTGGGCTGTGTGGGTGTGAGCCAGCTGGACCCACAGGTGGCCAGAGGAGACGTTCTGTGTACACACTCTGCCTAA
GCCCATGTGTGTCTGCAGAGACTCGGCCCGGCCAGCCACGATGGCCCTGCATTCCAGCCAGCCCGCACTTCATCACA
AACACTGACCCCAAAAGGACGGAGGTCTTGGCCACGTGGTCTGCCTGTCTCAGCACCCACCGGCTCACTCCCATGTG
TCTCCCGTCTGCTTTCGCAG

Intron 8 (SEQ ID NO 12)

10 GTGAGTCAGGTGGCCAGGTGCCATTGCCCTGCGGGTGGCTGGGCGGGCTGGCAGGGCTTCTGCTCACCTCTCTCCTGCC
CTTCCCCACTGNCCTTCTGCCCGGGGCCACAGAGTCTCCTTTCTGCCCCCGCCCCCTCCGGCTCCTGGGTGCAGGC
TCCCAGGGCCCCGAAACATGGCTCGGCTTGGCGCAGCCGGAGCGGAGCAGGTGCCACAGAGGCCTGGAAATGGCAAGC
GGGGTGTGGAGTTGCTCCTGCGTGGAGGACGAGGGGCGGGGGTGTGTCTGGGTGAGGTGTGCGCCGAGCGTTTGAGCCT
GCAGCTTGTGAGTCCAAGTTACTACTGACGCTGGACACCCGGCTCTCACACGCTTGTATCTCTCTCTCCGATACAAAA
15 GGATTTTATCCGATTCTCATTCCTGTCCCTGTGCTGTGACCCCCGCSAGGGCGGGGCTCTTCTCTCTGTGACTAGATTT
CCCATCTGGAAAGTGGGGTTGACCGTGTAGTTTGCTCCTCTCGGGGGGCTGTGGTGGCCATGGGGCAGGGCGGCTGG
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CTGGATTTTAAAGTAAACACACACCTCCCGGCAGGCATCTGCCCTGCGACCTGTGTGTGCTGGGAGAGTGGTAGCAC
GGAGGAAATTCGTGCACACTCAAGGTGATCAGCAAGGTGATCCGAGTCAGGTGGAACGTGGAGGCCTCTCTCTGGGATC
20 GTCTCCAGCGGATAAAGGACTGTGCACAGCTTCGGAAGCTTTTATTTAAAAATATAACTATTATTATGATTATAAGT
AATCACTAATGGTATCAGCAATTATAATATTTATTAAGTATAATTAGAAATATTAAAGTAGTACACAGTCTTGGA
CACAAATTGCACATGGCAGCAGAGTGAATTTTGGCCGAGGACACGCTGTGCACATGTGTGTAAGCGGCCCCAGGCCAC
AGAATTGCGTGACAAAGTCACCTCCCCAGAGAAGCCACCGGGCTCCTTCGTGGTGTGAATTTTATTAAGATGGATC
AAGTCACGTACCGTCCACGTGTGGCAGGGCTTTGGGGAATGTGAGGTGATGACTGCGTCTCATGCCCTGACAGACAGGA
25 GGTGACTGTGTCTGTCTGTCTCCTTAGGACACGGACAGGCCGGAAGCTCTAGTCCCATCGTGGTCCAGTTTGGCCTCTGA
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CTGTTGTCTGCTGGGCTTGAGTGCAGTGGCGGATCTCAACTCACTGCAACCTCCGCCTCCCGGGTCCAGCATTTCTC
30 CTGCCTCAGCCTCCCGAGCAGCTGAGATTACAGGCAACCCACCCCTGCGCCTGGCTAATTTTGTATTTTAGTAGAGAG
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GGATTACAGGTGTGAGCCATCACGCCAGCGGAAAGCCTCTTTTAAGGTGACCACCTATAGCGCTTCCGAAAATAAC
AGGTCTGTGTTTTGCACTAGGCTGCAAGCGTCTCTTAGCAACAGGAGTGGCGTCTGTGGGCTCTGGGATGGCTGAGGG
TCGGCTGGCAGCCATGCCTTCTGTGTGACCTTTAGGTTCACGGGGCTATTCTGCTCTCACTGTTTGTCTGAAAACGCA
35 CCCTTGGCATCCTTGTGAGAGATTCTGCTCTCGTTGGTGTGCTGAAACTAGGGGCAAGGTTGTATCCGTTGGCGC
GCAGCGGCTACATGTAGGTCATGAGTCTTACCGTGGACAAATTCCTTGAAAAAAGAGAGTCCGGTTAAGCAT
TCATTCCGGGTCAAGTGTCTGGTCTGTGAATAAATCTAAGATTTAAGAAACCTTAATGAAAGAAACCTTGATGATTC
AGAGCAAGGATGTGGTACACCTGTGGCTGGATCTGTTTCCAGCCGCCAGTGCATGGTGGAGTGGGAGGAGGATG
TTTGTTCAGAGGTCTCATCTGTGTATGTTTCTGAGGTGTTTGGCGGCTGAATGCTAGACGTGTGCTTGTGTGTATGAGGT
40 TGTGTGTCTGTCTGGCTCGGTTGAGTGTATGTCATGTCCAGCACATGCCCGGCCGCTCTCACCTGTGTCTTCCCGC
CCAG

Intron 9 (SEQ ID NO 13)

45 GTGAGGCCTCCTCTTCCAGGGGGCTTGGTGGGGGTTGATTTGCTTTGATGCATTCACTTTAATATTCCTGCTGC
TCTGGAGACCATGACTGCTGTGTCTGAGGAAACAACAAGGTTCAGACCCCTCTTGGTATGAAGCTGCACGGGAAGGG

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TTGCACAGCCTGAGGACTGCGGGCTCCACGAGGCTCTGTCCAGCGGCCATGTCCAGAGGCCTCAGGGCTCAGCAGGCGG
 GAGGGCCGCTGCCCTGCATGATGAGCATGTGAATCAACACCGAGGAAGCACACCAGCTTCTGTACCGTCACCCAGGTTT
 CGTTAGGGTCCTTGGGGAGATGGGGCTGGTGCAGCCTGAGGCCCCACATCTCCAGCAGGCCCTCGACAGGTGGCCTGGA
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 5 AACCTAATGTGGTTCAACTCAGCTGGCTTTTATTGACAGCAGTTACTTTTTTTTTTTAATACTTTAAGTTCTAGGGTAC
 ATGTGCACGAGTGCAGGTTAGTTACATATGTATACATGTGCCATGTTGGTGTGCTGCACCCATTAACTCATCATTTACA
 TTAGGTATATCTCCTAATGCTATCCCTCCCCACTCCCCCATCCCATGACAGGCCCTGGTGTGTGATGTTCCCCACCTG
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 10 CCGTGGTGTATATGTGCCACATTTCTTAATCCAGTCTATCATCGATGGACATTTGGGTTGGTTGCAAGTCTTTGCTACT
 GTGAATAGTGCCGCAATAACATACGTGTGCATGTGCTTTATAGCAGCATGATTTATAATCCTTTGGGTATATACCCAG
 TAATGGGATGGCTGGGTCAAATGGTATTCTAGTTCTAGATCCTTGAGGAATCACCACACTGTCTTCCACAATGGTTGAA
 CTAGTTTACACTCCCAACAGTGTAAAAGTGTCTGGTGTGGAGAGGATGTGGACAGCAGTTATTTTTTATGAAAA
 TAGTATCACTGAACAAGCAGACAGTTAGTGAAGGATGCGTCAGGAAGCCTGCAGGCCACACAGCCATTCTCTCGAAGAC
 15 TCCGGGTTTTTCCCTGTGCATCTTTTGAACTCTAGCTCCAATTATAGCATGTACAGTGGATCAAGGTTCTCTCTCATTAA
 GGTTCAGTTCTAGATTGAATAAGTTTATGTAACAGAAACAAAAATTTCTGTACACACAACCTGCTCTGGGATTGGGA
 GGAAAGTGTCTCGAGCTGGCGGCACACTGGTCAGCCCTCTGGGACAGGATACCTCTGGCCCATGGTCATGGGGCGCTGG
 GCTTGGCGCTGAGGGTCACACAGTGCACCATGCCAGCTTCTGTGGATAGGATCTGGGTCTCGGATCATGCTGAGGACC
 ACAGCTGCCATGCTGGTAAAGGGCACCACGTGGCTCAGAGGGGGCGAGGTTCCAGCCCCAGCTTTCTTACCCTCTTCAG
 20 TTATTTTTCCCTAAGAGTCTGAGAAGTGGGGCGCGCCTGATGGCCTTCGTTCTCTCAGCTGGCACAGAATTGCACAA
 CCTGATGGTAAACACTGAGTACTTATAATGAATGAGGAATTGCTGTAGCAGTTAACTGTAGAGAGCTCGTCTGTTGGAAA
 GAAATTTAAGTTTTTCATTTAACCGCTTTGGAGAATGTTACTTTATTTATGGCTGTGTAAATTGTTTGACATTCAAGTCCC
 TCGTAGACAGATACTACGTAAAAGTGTAAAGTTAACCTTGCTGTGTATTTCCCTTATTTTAG

25 **Intron 10 (SEQ ID NO 14)**

GTGAGGCCCGTGCCGTGTGTCTGTGGGGACCTCCACAGCCTGTGGGCTTTGCAGTTGAGCCCCCGTGTCTGCCCCCTGG
 CACCGCAGCGTTGTCTCTGCCAAGTCTCTCTCTGCGCGTGTGGATCCGCAAGAGCAGAGGCGCTTGGCCGTGCACC
 CAGGCCCTGGGGCGCAGGGGCACCTTCGGGAGGGAETGGGTACCGTGCAGGCCCTGGTCTGCAGAGACGCACCCAGGTT
 ACACACGTGGTGAGTGCAGGCGGTGACCTGGCTCTGTGCTCTTTGGAAAGTCAAGAGTGGCGGCTCCTGGGGCCCCAG
 30 TGAGACCCCCAGGAGCTGTGCACAGGGCTGCAGGGCCGAGGCGGCAGCCTCCTCCCCAGGGTGCACCTGAGCCTGCGGA
 GAGCAGGAGCTGCTGAGTGAGCTGGCCACAGCGTTCCGTGCGGTACGTTCTTGCCTGGGGTTGTTTGGGATCGGTGGG
 AGAATTTGGATTGCTGAGTGTGCTGTCTTGAACACGGAGATGGCTAGGAGTGGGTTTCAGAGTTGATTTTTGTGAAT
 CAAACTAAAATCAGGCACAGGGGACCTGGCCTCAGCACAGGGGATTGTCCAATGTGCTCCCCCTCAAGGGCGCCCCACAG
 AGCCGGTGGGCTTGTTTAAAGTGGATTTGACGAGGAGCAGAGAACCTTGAAAGCTGTAAAGGGAACCCCTCAGAAAAATG
 35 TGGCCGCCAGGGTGGTTTCAGTGCTTTGCTGGGCTGTGTTTGTGAAAACCCATTGAGACCCGCCCTCCAAGTCCACCC
 TCCAGGTCCACCTCCAGGGCCGCCCTGGGCTGGGGTATGCCTGGGCTTCCTTGTCTCGCAGCCCGGAGCACAGCAGGC
 TGTGCACATTTAAATCCACTAAGATTCACTCGGGGGAGGCCAGGTCCCAAGCAACTGAGGGCTCAGGAGTCTTGAGGCT
 GCTGAGGGGACAGAGCAGACCGGGAACGCTGCTCTGTGTGGCAAGTTCTGAGGGTCTGGCCAGGGAGGTGGCTCAGA
 GTGTATGTTGGGCTCCACCGGTGGCAGAATCTGTCTGTGATGAGTGGCAGCCATGTAAACAGGAAGGGGTGGCCACAG
 40 GGAGCTGGGAATGCACAGGGGAGCTGGCAGCTGGGCGAGGTCCAGGGCCAGGCCACAGGAAGGGCAGGGGGACGCC
 GGGGCCACAGCAGAGGCCCGAGGAAGGGAAGGGGATGCGCAGGCCAGAGCAGAGGCTACCGGGCACAGGGGGCTCCCTG
 AGCTGGGTGAGCGAGGCTCATGACTCGCGAGGGAACTCTCTTGACGTGAAGCTGAGTACTGGTGTGGCCAGCTCACA
 CCCAGCCAGGTCCCGGCCCTGACAGGAATCAGAAACCTCCCTTTGTCTAAAGCAAGCAGATGCCTTCAGGGCATCT
 AGGAGAAAACAGGCAAGTCTTGAGAACTGTCTTAAAGAGAGTGGGATGGTGGCAATTTCTGTCCAGATTTTAGTCT
 45 GCCCCGACACAGATGAGTCTATAACGGATTTGGTGTGTGCCATGGGGACACATGATGAGCCATCACAGAGGCCAG
 TGGGGCTGCAGCTCCCATGGAATCCTGGGTGTGCTGTGCGAGGCCAGGTTCTTATGCTCACCTACCTCTCCTGGC

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GGGAGACAGGGAAGCACCCCGAAGTCTGGAGCAGGGCTGGGTCCAGGCTCCTCAGAGCTCCTGCCAGGCCAGCACCCCT
GCTCCAAATCACCCTTCTCTGGGGTTTTCCAAAGCATTTAAACAAGGGTGTGAGGTTACCTCCTGGGTGACGGCCCCGCA
TCCTGGGGCTGACATTGCCCTCTGCCTTAG

5 **Intron 11 (SEQ ID NO 15)**

GTGAGCGCACCTGGCCGGAAGTGGAGCCTGTGCCCGGCTGGGGCAGGTGCTGCTGCAGGGCCGTTGCGTCCACCTCTGCT
TCCGTGTGGGGCAGGCGACTGCCAATCCCAAAGGGTCAGAGGCCACAGGGTGCCCTCGTCCCATCTGGGCTGAGCAGA
AATGCATCTTTCTGTGGGAGTGAAGGTGCTCACAAACGGGAGCAGTTTTCTGTGCTATTTTGGTAAAAGGAATGGTGCAC
CAGACCTGGGTGCACTGAGGTGTCTTCAGAAAGCAGTCTGGATCCGAACCCAGACGCCCCGGGCCCTGCTGGGCGTGAGT
10 CTCTCAAACCCGAACACAGGGGCCCTGTGGGCATGATCCCTCTGAACCCGAGACCCCTGGGGCCCTGCTGGGCGTGAGT
CTCTCCGAACCCAGAGACTTCAGGGCCCTTTTGGGCGTGAGTCTCTCCGCTGTGAGCCCCACACTCCAAGGCTCATCCAC
AGTCTACAGGATGCCATGAGTTCATGATCAGTGTGACCCATCAGGGGACAGGGCCATGGTGTGGGGGGGTCTCTACAA
AATTCTGGGGTCTTGTTCCTCCAGAGCCGAGAGCTCAAGGCCCGTCTCAGGCTCAGACACAAATGAATTGAAGATGGA
CACAGATGCAGAAATCTGTGCTGTTCTTTATGAATAAAAAGTATCAACATTCCAGGCAGGGCAAGTGGCTCACACCT
15 ATAATCCAGCACTTGGGAGGCCGAGGTGGGTGGATCACTTGAGGCCAGGAGTTGAGGCCAACCTAACCAACATAGTG
AAATTCCATTCTACTTAAAAAATACAAAAATTAGCCTGGCCTGGTGGCACACGCTGTAGTCCCCGTATGCGGGAGGC
TGAGGCAGGAGAATCATTTGAACCCAGGAGGCAGAGGTGCACTGAGCCGAGATCACACCACTGCACTCCAGCCTGGGCA
ACAGAGTGAGACTTCATCTAAAAAATAAAAAAAGTATCAGCATTCCAAAACCATAGTGGACAGGTGTTTTTTATTC
TGTCCTTCGATAATATTACTGGTGTCTGTCTAGAGGCCGGAATGGGGTGCCTTCCTCTGAAAGGCACACCTTCATGG
20 GAAGAGAAATAAGTGGTGAATGGTGTGTTAAACCAGAGGTTTAAACTGGGGTCTGTGCTTCTGAGTTAACAGTCCAGATC
TGGACTTTGCTCTTTCCAGAATGCTCCCTGGGGTTTGCTTCATGGGGGAGCAGCAGGTGTGGACACCTCGTGATGGGG
GAGCAGCAGGTGCAGACGCCCTCATGATGGGGAGTGGCAGGTGCAGACACCTTGTGCATGTTGCCAGCATGTCCCTG
TTGCAGCTCCCTCCCAAGGATGCCGGTCTCCTGTGCTCCCAAGTCCCTGCTCCCTCTCACAGCCTTACCTGGTC
CTGGCTCCACTGGCTTTGTCTGCATGATTTCCACATTTCCCTGGGCTCCCAAGCCTCTTCGCTCTCCCAAGCCTCT
25 GCAGTCTGGCCATACCACTGAGGTGTGAAGTGTCCACTGCTTATTTGCTCCCATGAAATGATTTTTTAGGACAGGC
ACCCCTGGTTCCAGCCTCTGGCACAGCATCAGTGAATGTTATTGAAGGACAAAGGACAGACAAACAAATCAGGAAATGG
GTTCTCTCTAAACACATTGCAAAGCCACAGAGGCTAGTGACAGGATGGGTGGGCATCAGGTCTCAGATGTGGGTCCAATG
CCAGAATATTCTGTGCTCCCAAAGGCCACTTGGTCAGAGTGTGTGCTTGACAGGTGGCTCTAAAAGCTCAGCAGTGGAG
GCAGTGGTTGCGCATACTCAGGGTGAACACATCCTCTGTGTCTGAAGTATACAGCAGAGGCTTGAAGGGCATCTGGGA
30 GAAGAAAACAGGCCAAATGATTAAAGAAAGTGAAGAAAGGAAAGTGGTAAGATGGGAATTTCTTGTCCAGATTTTAGTC
TCCCAAACACAGCTCAGATGTTAGTGTGGTGAAGTGTGACAGAACTAGTGAACAAACGGAAGCCCTATCTCT
CAGAAACGTGTGTTAATGTGGTATGTGGCACAGCTGATGGAAGAGAGTGTGTGTGTAATTTTTTTTCTGAGAAAATC
GACTGGAAGCAAATAAGTTGTCTTTACAGCATATACCAGAGCAGATTCTAGGTAGAAGAGGAGACACATGCAAACAAC
ACCAGCAACAGAAATAAAACAAAGACTCAAAGGGAAGGGAGGTGAACGTTCCCTGGTTTGGTGTGGGGAAGGACACAC
35 AGGGAGGCGGATGAAACCACTGAGGCAACGGGCATTGCTTCACTGCAGAGAACTCAGCTTGCTGAGCCACAGTGAAG
ATGGCCATTCCCTGGAGCGTTTGTGACGTGATTATTTAAGGCGCCCTGTGAGGTCTGCACATTCTCCTCTCACTTT
GTTCTCCTAACACCTGAGAGGTAGAGGAGGAAGGCTCCAGGGGAGCAGCGGCCCTGGTCAACCAGCTGGCAAAGGGC
ATGCATGATTGCAGCCTGGCTTCTGCTCCGGGGCCCTGTCTGCCCCAGGACCCACACAAGTCAGACCCATAGGCTC
AGGGTGAGCGGAGCCCAAGGTGTGTTGGGATGGCTGTGAAAGAAGAATGGACGTCTGATGCACACTTGGGAAGGTC
40 CTACCAGCAGCGTCAAAGAAATCTATGTGAAATGACAGCGAGACCCATCCCTCAAAGAAACGCAGTGAAGTGTATGGC
TAGACCTGTCCCATCCCTCATCTGGCTCCTTTCTGGGTTTGCCAGAGCCAGCATCAGTTGAGGCAAGCTGGAAG
ACTTTCTGGAAGCAGCTTGTGTGATGGAATGCTCACAATGTCTGTGCTTCCCACTAATCCACTTCTGAAGTGA
CCAGACATTATCAGGGTCTTATTTACCATTCAGTGTTCAGGCAGGGGACTTGCACAGCAAGTCACGAACCTGCC
TAAATACAGGGCTAAGGAGATATTATGCATCAAAAACTTCTCTGCCATTAAACATTTTCAAAGAAATTTTGAAGAA
45 TTTTAAATGGCACAAACGTTTATTTCAATGTAGTGTGTTAAAGCTGGATGTAAAGAACACACCCAGGAGCCTGCCG
GCAATGTCTGTGTCTTCTCATCTTGGACATGTAATACATGGCAGTGAATGGTGGTGAAGGCCCTGGAGGACATCGGTGG

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GATGCCTCCATCCTGCCCTCTGGAGACACCATGTGTGCCACGTGCACTCACTGGAGCCCTGTTTAGCTGGTGCCACCTG
 GCTCTTCCATCCCTGAGATTCAAACACAGTGAGATTCCCCACGCCCAACTCAGTGTCTCCACAAAAAACCTGAGTCAC
 ACCTGTGTTCACTCGAGGGACGCCCGGGAGCCAGGGCTCCACAGTTTATTATGTGTTTTTGGCTGAGTTATGTGCAGATC
 TCATCAGGGCAGATGATGAGTGACAAACACGGCCGTGCGAGGTTTGGATACACTCAACATCACTAGCCAGGTCTGTGGT
 5 GAGTTTTGGTCATGCAGAGTCTGGATGGCATGTAGCATTTGGAGTCCATGGAGTGAGCACCAGCCCCCTCGGGCTGCAGC
 GCATGCCCCAGGCAGGACAAGGAAGCGGAGGAAGGCAGGAGGCTCTTTGGAGCAAGCTTTGCAGGAGGGGGCTGGGTGT
 GGGGCAGGCACCTGTGTCTGACATTCCCCCTGTGTCTCAG

Intron 12 (SEQ ID NO 16)

10 GTGAGCAGGCTGATGGTCAGCACAGAGTTCAGAGTTCAGGAGGTGTGTGCGCAAGTATGTGTGTGTGTGTGCGCGCGT
 GCCTGCAAGGCTGATGGTGACTGGCTGCACGTGAAGAGTGACATGTACGCATATACACGTGAGCACATACATGTGTGCAT
 GTGTGTACATGAAGGCATGGCAGTGTGTGCACAGGTGTGCAAGGGCACAAGTGTGTGCACATGCGAATGCACACCTGACA
 TGCATGTGTGTTCTGTGCACAGTCTGTGGGCATTACGTGAGGTGCATGCGTGTGGGTGTGCAGTGTGAGTAGCATGTGT
 GCACATAACATGTATTGAGGGGTCTCTGTGTTACCCCGCTAGGTCCTCAGCACCAGTGCCACTCCTTACAGGATGAGAC
 15 GGGGTCCCAGGCTTGGTGGGTGAGGCTCTGAAGTGCACGCCCTGAGGGCATTGTCCCCTCTGGGCATCCGCGTCCACT
 CCTCTCCTGTGGGCTTCTGTGTCCACTCCCCCTCTCCTGTGGGCATTTACATCCACTCCACTCCCTCTCTCCTGTGGGC
 ATCCGCGTCCACTCCCCCTCTCTGTGGGCATCTGGTCCACTCCCCCTCTCTGTGGGCATTTGCGTCCACTCCCTCTCCT
 GGTTCCTTCTGTCTTGGCCGAGCCTCGGGGCAGGCAGATGACACAGAGTCTTGACTCGCCAGGGTGGTTCGCAGCTG
 CCGGGTGAAGGCCAGGCCGATTCTACTGGGAAGAGGGATAGTTTCTTGCAAAATGTTCTTCTTCTTGTCCATCTGA
 20 ATGGATGATAAAGCAAAAAGTAAAACTTAAATCCCAGAGAGGTTTCTACCGTTTCTCACTCTTCTTGGCGACTCTAG

Intron 13 (SEQ ID NO 17)

GTGAGCCGCCACCAAGGGGTGCAGGCCAGCCTCCAGGGACCCCTCCGCGCTCTGCTCACTCTGACCCGGGGCTTCACCT
 TGAAGCTCCTGGGTTTTAGGGGCAAGGAATGTCTTACGTTTTCACTGGTGCTGCTGCCTGTGCACAGTTCTGTTCCGCGT
 25 GCTCTGTGCAAAAGCACCTGTCTCCATCTCTGGGTAGTGGTAGGAGCCGGTGTGGCCCCAGGTGTCCCCACTGTGCCTGT
 GCACTGGCCGTGGGACGTTCATGGAGGCCATCCAGGGCAGCAGGGGCATGGGGTAAAGAGATGTTTATGGGGAGTCTTAG
 CAGAGGAGGCTGGGAAGGTSTCTGAACAGTAGATGGGAGATCAGATGCCCGGAGGATTGGGGTCTCAGCAAAGAGGGCC
 GAGGTGGGTGCAGGTGAGGGTCTGTGGCCCCACCCCGGGAAGGTGCAGCAGAGCTGTGGCTCCCCACACAGCCCGGCCA
 GCACCTGTGCTCTGGGCATGGCTGTCTCTGGAACGTTCCCTGTCTGGCTGGTCAGGGGTGCCCTGCCAAGAATCG
 30 ACAACTTTATCAGAGGGGAAGGGCCAATCTGTGGAGGCCACAGGGCCAGCTTCTGCTGGAGTCAGGGCAGGTGGTGGC
 ACAAGCCTCGGGCTGTACCAAAGGGCAGTCGGGCACCACAGGCCCGGGCTCCACCTCAACAGGCCTCCCGAGCCACTG
 GGAGCTGAATGCCAGGAGGCCGAAGCCCTCGCCCCATGAGGGCTGAGAAGGAGTGTGAGCATTTGTGTTACCCAGGGCCG
 AGGCTGCGCGAATTACCGTGCACACTTGATGTGAATGAGGTCTGCTCTATCGTGGAAOCCAGCAAGGGCTCACGGGA
 GAGTTTTCCATTACAAGGTCTGACCATGAAAATGTTTTTAAACCGAGTGCTTGGCCTTCATGCTCTGGCAGGGAGGGC
 35 AGAGCCACAGCTGCATGTTACCGCCTTTCACCAAGCTCCAGAGGCTTGGGACCAGGCTGTCTCAGTTCACAGGTGCGTCC
 GGCTCAGACCGCCCTCCTCTCTGCTCTCTCTCTCTGCTCAAATTTCCCTCGTTTGCATCTCCCTGACGCGTGCCTGGG
 CCTCTGTGCAAGCTGCTTGAATCCTTTCCGGAAACCTTGGGGTGTGCTGATACAGGTGCCACTGAGGACTGGAGGTGT
 CTGACACTGTGTTTACCCCGAGGGTCCAGCTGGGCTGCTTGGGGCTCCTTGGGCCATGATGAGGTGAGAGGAGTTTCC
 CAGGTGAAAACCTCGGGAACTCCGAGGGCATGTGACCTGCACTGCTCTCCCATATTCACTCAGTCTTGTCTCTC
 40 ATTTCCCAACCGGGTCTCTAGCTCCGAGGAGCTCCCGTAGAGGGCTTGGTCCAGGGCAGGGCGCTGAGTTTCCCCAC
 CCATGCGGGGACCTTGGGTAGTCTCTTGAATTCCTAGCCCTGAGGAGGCTGAGTGGCATGGGCCAGGGCCGTTTCCA
 AACACAGAGTGCAGGCAGTGGAGGCCGAGGAATCCCTTCCCTTGAAGGATGAGTGGGAGAACGGAGAGCTGGGCCCG
 ATTTACGGGATCCAGGCTGCACTGGGAGGCTTGGTGGTGCAGGTGGGCTGGGGCGGGGTCTGATTCAAAATCCGC
 TGGGGCTGGGCTTCTGTGGCCCTTGTGGCCGCTCTCCACAGGCTGAGGCTGGGCTGGGCTGGGCTGGGCTGGGCTGGG
 45 TATTTCTCCCTTGGGAAGAGAGCTCTCACCCATGCTAGGTGTTTCCCTCTGGGTGAGGAGCTGGCCGTGTGGCAACC

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CCGGGACCTTAGGCTTATTTATTTGTTTAAAAACATTCTGGGCTGGCTTCCGTTGTTGCTAAATGGGAAAAGACATCC
 CACCTCAGCAGAGTTACTGAGAGGCTGAAACCGGGGTGCTGGCTTGAAGTGTGATCTCAGGTCATTCCAGAAGTGGCT
 CAGGAAGTCAGTGAGACCAGGTACATGGGGGGCTCAGGCAGTGGGTGAGATGAGGTACACGGGGGGCTCAGGCAGTGGGT
 GAGGCCAGGTACATGGGGGGCTCAGGCAGTGGGTGAGATGAGGTACACGGGGGGCTCAGGCAGAGGGTACAGCCAGGTAC
 5 ACGGGGGCTCTGATCACACGCACATATGAGCACATGTGCACATGTGCTGTTTCATGGTAGCCAGGTCTGTGCACACCTGC
 CCCAAAGTCCCAGGAAGCTGAGAGGCCAAAGATGGAGGCTGACAGGGCTGGCGCGGTGGCTCACACCTGTAGTCCCAGCA
 CTTTGGGAGGCCGAGGCGAGAGGATCCCTTGAGCCCAGGAGTTTAAGACCAGCCTGAGCAACATAGTAGAACCCCATCTC
 TATGAAAAATAAAAAACAAAATTAGCTGAACATGGTGGTGTGCGCCTGTAGTTCCAATACTTGGGAGGCTGAAGTGGGAG
 GATCACTTGAGCCCAGGAGGTGGAAGCTGCAGTGAGCTGAGATTGCACCACTGTACTGCAGCCTGGGTGACAGAGTGAGA
 10 GCCATCTCAACAACAACAAGAAGACTGACAAATGCAGTTTCTTGAAAGAAACATTAGTAGGAACTTAACCTACACA
 CAGAAGCCAGTCCGTGTCTCGGTGTGAGTGTGAGATGATGGGTCTCACACCATCACCCAGACCCAGGGTTTATG
 CACCACAGGGGGCGGTGGCTCAGAAGGGATGCGCAGGACGTTGATATACGATGACATCAAGTTGTCTGACGAAGGGCAG
 GATTGATGATAAGTACCTGCTGGTACACAAGGAACAATGGATAAACTGGAAACCTTAGAGGCCCTCCCGAACAGGGGCT
 AATCAGAAGCCAGCATGGGGGGCTGGCATCCAGGATGGAGCTGCTTCAGCCTCCACATGCGTGTTCATACAGATGGTGCA
 15 CAGAAACGCAGTGATCTGTGCACACACAGACACGCAGTACTCGCACACACAAGCACACACAGACATGCATGCATGC
 ATCCGTGTGTGTGCACCTGTGCCCATGAGGAAACCCATGCATGTGCATTGATGCACGCACACAGGCACCGGTGGGCCAT
 GCCCACACCCACGAGCACCGTCTGATTAGGAGGCCCTTCTCTGACGCTGTCCGCCATCCTCTCAG

Intron 14 (WEQ ID NO 18)

20 GTATGTGCAGGTGCCTGGCCTCAGTGGCAGCAGTGCCTGCCTGCTGGTGTAGTGTGCAGGAGACTGAGTGAATCTGGG
 CTTAGGAAGTCTTACCCCTTTTCGCATCAGGAAGTGGTTTAAACCAACCACTGTGAGGCTCGTCTGCCGCCCTCTCGT
 GGGGTGAGCAGAGCACCTGATGGAAGGGACAGGAGCTGTCTGGGAGCTGCCATCCTTCCACCTTGTCTGCTGGGGAA
 GCGCTGGGGGGCTGGTCTCTCTGTTTCCCCATGGTGGGATTTGGGGGGCTGGCTCTCTGTTTGGCCTGTGGTGG
 GATTGGGCTGTCTCCCGTCCATGGCACTTAGGGCCCTTGTGCAAAACCCAGGCCAAGGGCTTAGGAGGAGGCCAGGCCAG
 25 GCTACCCACCCCTCTCAGGAGCAGAGGCCGCTATCACACGACAGAGCCCGCGCGCTCTCTGCTTCCAGTCAACG
 TCCTCTGCCCTGGACACTTTGTCCAGCATCAGGGAGGTTTCTGATCCGTCTGAAATTCAGCCATGTCGAACCTGCGGT
 CCTGAGCTTAACAGCTTCTACTTTCTGTTCTTCTGTGTTGTGGAAATTCACCTGGAGAAGCCGAAGAAAACATTCTG
 TCGTGACTCCTGCGGTGCTTGGGTGCGGACAGCCAGAGATGGAGCCACCCCGCAGACCGTCCGGTGTGGGCAGCTTCCG
 GTGCTCTCTGGGAGGGGAGCTGGGCTGGGCTGTGACTCCTCAGCCTCTGTTTCCCCCAG

Intron 15 (SEQ ID NO 19)

GCAAGTGTGGGTGGAGGCCAGTGGCGGGCCACCTGCCAGGGGTGATCCTTGAACGCCCTGTGTGGGGCAGCAGCCTC
 AGATGCTGTGAAGTGACAGCGCCCCGGGCTGACCTGGGGGCTGGAGCCACGCTGGCAGCCCTATGTGATTAACG
 CTGGTGTCCCCAGGCCACGAGCCTGGCAGGCTCCCAACTTCTTGAACCCCTGCTTCCATCTCAGGGGCGATGGCTCC
 35 CCACGCTTGGGAGCCTTCTGACCCCTGACCTGTGCTCTCACAGCCTCTTCCCTGGCTGCTGCCCTGAGCTCCTGGGT
 CCTGAGCAAGTTCTCTCCCGCCCCGGCTCCAGCGTCACTGGGCTGCCTGTCTGCTGCGCCCGGTGAGGGGTGTCTG
 TCCCTTCACTGAGGTTCCACACAGCCAGGGCCAGAGGTGACAGGCCCTGCCTGCCCGGCCACCCACACGTCCTAGGAGGG
 TTGGAGGATGCCACCTCTGGCTCTTCTGGAACGAGTCTGATTTGGCCCCGAG

3'-untranscribed region (SEQ ID NO 20)

40 ATCTCATGTTTGAATCCTAATGTGCACTGCATAGACACCACTGTATGCAATTACAGAAGCCTGTGAGTGAACGGGGTGGT
 GCTCAGTGGCGGGCCATGGCCTGGCTGTGCAATTACGGAAGTCTATGAGTGAATGGGGTTTGGTTCAGTGGCGGGCCATG
 GCCTGGCTGGGCTGGGAGGTTTCTGATGCTGTGAGGCAGGAGGGGAAGGAGGTAGGGGATAGACAGTGGGAGCCCCCA
 CCTGGAAGACATAACAGTAAGTCCAGGCCCAAGGGCAGCAGGATGCTGGGGGCCAGCTTGGGCGCGGGGATGATG
 45 GAGGGCTGSCCAGGGTGGCAGGATGATGGGGGCCAGCTGGGCTGGCAGGGGTGATGGGCGGGGTGTGCTGGGTGG

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CGGGGAAGATGGGAAGCCTGGCTGGGCCCCCTCCTCCCTGCCCTCCACCTGCAGCCGTGGATCCGGATGTGCTTCCCT
 GGTGCACATCCTCTGGGCCATCAGCTTTTCATGGAGGTGGGGGGCAGGGGCATGACACCATCCTGTATAAAATCCAGGATT
 CCTCCTCTGAACGCCCCAACTCAGGTTGAAAGTCACATTCCGCCTCTGGCCATTCTCTTAAGAGTAGACCAGGATTCTG
 ATCTCTGAAGGTGGGTAGGGTGGGGCAGTGGAGGGTGTGGACACAGGAGGCTTCAGGGTGGGGCTGGTGATGCTCTCTC
 5 ATCCTCTTATCATCTCCAGTCTCATCTCTCATCTCTTATCATCTCCAGTCTCATCTGTCTTCTCTTATCTCCAGT
 CTCATCTGTCTATCCTTTACCATCTCCAGTCTCATCTCTTATCCTCTTATCTCTTAGTCTCATCCAGACTTACCTCCCA
 GGGCGGGTCCAGGCTCGCAGTGGAGCTGGACATACGTCCTTCCTCAGGCAGAGGAACTGGAGGATTGCAGAGAACAG
 GAGGGCGGGCTCAGAGGGACGCAGTCTTGGGGTGAAGAAACAGCCCCCTCCTCAGAAAGTTGGCTTGGGCCACACGAAACCG
 AGGGCCCTGCGTGAGTGGCTCCAGAGCCTTCAGCAGGTCCCTGGTGGGGCTTATGGTATGGCCGGTCCCTACTGAGTG
 10 CACCTTGGACAGGGCTTCTGGTTTGAGTGCAGCCCGGACGTGCCTGGTGTGGGGTGGGGCTTATGGCCACTGGATATG
 GCGTCATTTATTGCTGCTGCTTCAGAGAATGTCTGAGTGACCGAGCCTAATGTGTATGGTGGGCCCAAGTCCACAGACTG
 TGTCTAAATGCACCTCTGGTGCCTGGAGCCCCGTATAGGAGCTGTGAGGAAGGAGGGGCTCTTGGCAGCCGGCTGGGG
 GCGCCTTTGCCCTGCAAACTGGAAGGGAGCGCCCCGGCGCCGTGGGCGGACGACCTCAAGTGAGAGGTTGGACAGAAC
 AGGGCGGGGACTTCCAGGAGCAGAGGCGCTGCTCAGGCACACCTGGGTTTGAATCACAGACCAACAGGTACAGGCCATT
 15 GTTCAGCTATCCATCTTCTACAAAGCTCCAGATTCTGTTTCTCCGGGTGTTTTTGTGAAATTTTACTCAGGATTACT
 TATATTTTTTGTCTAAAGTATTAGACCTTAAAAAAGGTATTTGCTTTGATATGGCTTAACTCACTAAGCACCTACTTTAT
 TTGTCTGTTTTTATTATTATTATTATTATTATTAGAGATGGTGTCTACTCTGTCAACCAGGTTGTTAGTGCAGTGGCAC
 AGTCATGGCTCGCTGTAGCCGCAAAACCCAGGCTCAAGTGATCCTCGGCCTCAGCTTCCAGAGTGTGGGATTACAG
 GTGTGAGCCACTGCCCTTGCTGGCACTTTTAAAAACCCTATGTAAGGTGAGTCCAGTGGCTTCCACACCTGTCTATCC
 20 CAGTAGTTTGGGAAGCCGAGGCAGAAGGATTGTCTGAGGCCAGGAGTTTGAAGCCAGCATGGGTAACATAGGGAGACCCC
 ATCTCTACAAAAAATGCAAAAAGTTATCCGGGGCTGGGGTCCAGCATCTGTAGTCCAGCTGCTCGGGAGGCTGAGTGGG
 AGGATCGCTTGAGCCCGGGAGGTGATGGCTGCAGTGCAGTGTGATTGTAACATCGCACTCCAGCCTGGGCAACAGAGTGA
 GACCTGTCTCAAAAAAAAAAAAAAAAAAGAGGAGAGGAGAGAAGAGAAGAAGGAAGGAAGGAAGGAAGGAAGGAAG
 GAAGAAGGAAGAAAGAGGAGAGGAGGCTGCTAGGTGCTAGGTAGACTGTCAAATCTCAGAGCAAAATGAAATAACA
 25 AAGTTTTAAAGGGAAAGAAAAACCCAGCTCTTTGGACTTCCTTAGGCCTGAACCTCATCTCAAGCAGCTTCTTCCACA
 GCAAGCGTGTATGGAGCGAGTCAAGTCAAAGCAGAAAGGGAGGAGAGCAGGCAAGGGTGGAGGCTGTGGGTGACACCA
 GCCAGGACCCCTGAAAGGGAGTGGTTGTTTTCTGCTCAGCCCCACGCTCCTGCCGGTCTGCACCTGCTGTAACCGTC
 GATGTTGGTGCCAGGTGCCACCTGGGAAGGATGCTGTGCAGGGGGCTTGCCAACTTTGGTGGGTTTCAGAAGCCCCAG
 GCCTTGTGGCAGGCACAATTACAGCCCTCCCAAAGATGCCACGTCCTTCTCCTGGAACCTGTGAATGTGTCAACCG
 30 CAAGGCAGAGGCTGGTGAAGGCTGCAGGTGGAATCACGGCTGCCAGTCAGCCGATCTTAAGGTCATCTGGATTATCTGG
 TGGGCTGATATGGCCACAAGGGTCCCTAGAACTGAGAGAGGGAGGCAGGGGAGAGTCAGAGAGGGGACGTGAGAAGGAC
 CACTGGCCACTGCTGGCTTTGAGATGGAGGAGGGGTCCCCAGCCAAGGAATGGGGCAGCCGCTCCATGCTGGAAAAAGC
 AAGCAATCCTCCCGGTCTGAGGGCACAGGGCCCTGCCACGCTCGATTTCAGGCCAGTGGGACCTGTTTCAGCTTTC
 CGGCCTCCAGAGCTGTAAGATGATGCGTTTGTGTTACGCCACTAAGCTGCAGTGATTGCTCACAGCAGCAATGGAATAG
 35 CAGTACAGGGAATGAATACAGGGACAGTTCTCAGAGTGACTCTCAGCCCCCCCTGGG

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Characterization of the exons showed, interestingly, that the functionally important hTC protein domains which are described in our Patent Application PCT/EP/98/03469 are arranged on separate exons. The telomerase-characteristic T motif is located on exon 3. The RT (reverse transcriptase) motifs 1-7, which are
5 important for the catalytic function of the telomerase, are located on the following exons: RT motifs 1 and 2 on exon 4, RT motif 4 on exon 9, RT motif 5 on exon 10, and RT motifs 6 and 7 on exon 11. RT motif 3 is shared by exons 5 and 6 (see Fig. 8).

10 Elucidation of the exon-intron structure of the hTC gene also shows that the four deletions or insertion variants of the hTC cDNA which were described in our Patent Application PCT/EP/98/03469, as well as three additional hTC insertion variants which are described in the literature (Kilian et al., 1997), in all probability represent alternative splicing products. As shown in Fig. 8, the splicing variants can be divided
15 into two groups: deletion variants and insertion variants.

The hTC variants in the deletion group lack specific sequence segments. The 36 bp in-frame deletion in variant DEL1 in all probability results from using an alternative 3' splice acceptor sequence in exon 6, resulting in a part of RT motif 3 being lost. In
20 variant DEL2, the normal 5' splice donor and 3' splice acceptor sequences of introns 6, 7 and 8 are not used. Instead exon 6 is fused directly to exon 9, resulting in a displacement arising in the open reading frame and a stop codon appearing in exon 10. Variant Del3 is a combination of variants 1 and 2.

25 The insertion variant group is characterized by the insertion of intron sequences which lead to premature cessation of translation. Instead of the 5' splice donor sequence of intron 5, which is normally used, use is made, in variant INS1, of an alternative, 3'-located splice site, resulting in the insertion of the first 38 bp from intron 4 between exon 4 and exon 5. The insertion, in variant INS2, of a region of the
30 intron 11 sequence likewise results from using an alternative 5' splice donor sequence in intron 11. Since this variant was only described inadequately in the

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literature (Kilian et al., 1997), it is not possible to determine the precise alternative 5' splice donor sequence in this variant. The insertion of intron 14 sequences between exon 14 and exon 15 in variant INS3 comes from using an alternative 3' splice acceptor sequence, resulting in the 3' part of intron 14 not being spliced.

5

The hTC variant INS4 (variante 4), which is described in our Patent Application PCT/EP/98/03469, is characterized by exon 15, and the 5' part region of exon 16, being replaced by the first 600 bp of intron 14. This variant can be attributed to the use of an alternative internal 5' splice donor sequence in intron 14 and an alternative

10

3' splice acceptor sequence in exon 16, resulting in an altered C terminus.

The *in vivo* generation of hTC protein variants which are probably non-functional and which could interfere with the function of the complete hTC protein constitutes a possible mechanism, in addition to transcription regulation, for controlling hTC protein function. The function of the hTC splicing variants is not yet known. Although most of these variants presumably encode proteins without reverse transcriptase activity, they could nevertheless play a crucial role as transdominant-negative telomerase regulators by, for example, competing for interaction with important binding partners.

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The search for possible transcription factor binding sites was carried out using the „find pattern“ algorithm from the Genetics Computer Group (Madison, USA) GCG Sequence Analysis program package. This resulted in the identification of a variety of potential binding sites for transcription factors in the nucleotide sequence of intron 2, which binding sites are listed in Tab. 2. In addition, an Sp1 binding site was found

25

in intron 1 (pos. 43), and a c-Myc binding site was found in the 5'-untranslated region (cDNA position 29-34, cf. Fig. 6).

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Example 6

In order to ascertain the start point(s) of hTC transcription in HL 60 cells, the 5' end of the hTC mRNA was determined by means of primer extension analysis.

5 2 µg of polyA⁺ RNA from HL-60 cells were denaturated at 65°C for 10 min. 1 µl of
RNasin (30-40 U/ml) and 0.3-1 pmol of radioactively labelled primer
(5'GTAAAGTTGTAGCTTACACTGGTTCTC 3'; 2.5-8x10⁵ cpm) were added for
primer annealing, and the whole was incubated, at 37°C for 30 min, in a total volume
10 of 20 µl. After the addition of 10 µl of 5xreverse transcriptase buffer (from Gibco-
BRL), 2 µl of 10 mM dNTPs, 2 µl RNasin (see above), 5 µl of 0.1 M DTT (from
Gibco-BRL) 2 µl of ThermoScript RT (15 U/µl; from Gibco-BRL) and 9 µl of
DEPC-treated water, primer extension took place, at 58°C for 1 h, in a total volume
[lacuna]. The reaction was stopped by adding 4 µl of 0.5 M EDTA, pH 8.0, and the
15 RNA was degraded, at 37°C for 30 min, after having added 1 µl of RNaseA
(10 mg/ml). 2.5 µg of sheared calf thymus DNA and 100 µl of TE were then added,
and the mixture was extracted once with 150 µl of phenol/chloroform (1:1). The
DNA was precipitated, at -70°C for 45 min, after adding 15 µl of 3 M Na acetate and
450 µl of ethanol, and then centrifuged at 14,000 rpm for 15 min. The precipitate was
20 washed once with 70% ethanol, dried in air and dissolved in 8 µl of sequencing stop
solution. After 5 min of denaturation at 80°C, the samples were loaded onto a 6%
polyacrylamide gel and fractionated electrophoretically (Ausubel et al., 1987)
(Fig. 5).

25 In this connection, a main transcription start site was identified which is located
1767 bp 5' of the ATG start codon of the hTC cDNA sequence (nucleotide position
3346 in Fig. 4). In addition to this, the nucleotide sequence around this main
transcription start (TTA_nTTGT) represents an initiator element (Inr), which, in 6 out
of 7 nucleotides, matches the consensus motif (PyPyA_nNa/tPyPy) (Smale, 1997) of
30 an initiator element.

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It was not possible to identify any unambiguous TATA box in the immediate vicinity of the experimentally identified main transcription start, which means that the hTC promoter has probably to be classified in the family of TATA-less promoters (Smale, 1997). However, a potential TATA box from nucleotide position 1306 to nucleotide position 1311 (Fig. 4) was found by means of bioinformatics analysis. The subsidiary transcription starts which were additionally observed around the main transcription start have also been described in the case of other TATA-less promoters (Geng and Johnson, 1993), for example in the strongly regulated promoters of some cell cycle genes (Wick *et al.*, 1995).

Example 7

In addition to the start point of the hTC transcript which was described in Example 6 and identified in HL60 cells, a further transcription start region was also identified in HL60 cells. With the aid of RT-PCR analyses, the region of the hTC gene transcription start in HL60 cells was localized to bp -60 to bp -105.

The cDNA for this was synthesized using a First Strand cDNA Synthesis kit (Clontech), in accordance with the manufacturer's instructions, and employing 0.4 µg of HL60 cell polyA RNA (Clontech) and the gene-specific primer GSP13 (5'-CCTCCAAAGAGGTGGCTTCTTCGGC-3', cDNA position 920-897). In a final volume of 50 µl, 10 pmol dNTP mix were added to 1 µl of cDNA, and a PCR reaction was carried out in 1xPCR reaction buffer F (PCR-Optimizer kit from InVitrogen) and using one unit of platinum Taq DNA polymerase (from Gibco/BRL). 10 pmol of each of the 5' and 3' primers defined below were added as primers. The PCR was carried out in 3 steps. A two-minute denaturation at 94°C was followed by 36 PCR cycles in which the DNA was first of all denatured at 94°C for 45 sec and, after that, the primers were annealed, and the DNA chain was extended at 68°C for 5 min. The cycles were concluded by a chain extension at 68°C for 10 min. In all, six different 5' PCR primers (primer HTRT5B: 5'-CGCAGCCACTACCGCGAGGTGC-3', cDNA position 105 to 126; primer C5S:

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5'-CTGCGTCCTGCTGCGCACGTGGGAAGC-3', 5'-flanking region -49 to -23; primer PRO-TEST1: 5'-CTCGCGGCGCGAGTTTCAGGCAG-3', 5'-flanking region -74 to -52; primer PRO-TEST2: 5'-CCAGCCCCTCCCCTTCCTTTCC-3', 5'-flanking region -112 to -91; primer PRO-TEST4: 5'-CCAGCTCCGCCTCCTCCGCGC-3', 5'-flanking region -191 to -171; primer RP-3A: 5'-CTAGGCCGATTCGACCTCTCTCC-3', 5'-flanking region -427 to -405) were combined with the 3' PCR primer C5Rback (5'-GTCCCAGGGCAGCACACCAG-3', cDNA position 245 to 225). Genomic DNA was also employed for the PCR, as a control, in addition to the Oligo dT- and GSP13-primed cDNAs. As Fig. 9 shows, a PCR product was only obtained with the primer combinations HTRT5B-C5Rback, C5S-C5Rback and PRO-TEST1-C5Rback, indicating that the start point for hTC transcription lies in the region between bp-60 and bp-105.

15 Example 8

Several extremely GC-rich regions, so-called CpG Islands, are located in the isolated 5'-flanking region, of about 11.2 kb in size, of the hTC gene. One CpG Island, having a GC content of > 70%, extends from bp -1214 into intron 2. Two further GC-rich regions having a GC content of > 60% extend from bp -3872 to bp -3113 and from bp -5363 to bp -3941, respectively. The positions of the CpG Islands are shown graphically in Fig. 11.

The search for possible transcription factor binding sites was carried out using the "Find Pattern" algorithm from the Genetics Computer Group (Madison, USA) GCG Sequence Analysis program package. This resulted in the identification of a variety of potential binding sites in the region up to -900 bp upstream of the translation start codon ATG: five Sp1 binding sites, one c-Myc binding site, and one CCAC box (Fig. 10). In addition, a CCAAT box and a second c-Myc binding site were found at positions -1788 and -3995, respectively, of the 5'-flanking region.

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Example 9

In order to analyse the activity of the hTC promoter, PCR amplification was used to generate four hTC promoter sequence segments of differing length, which segments were cloned into the Promega vector pGL2 5' in front of the luciferase reporter gene.

5 The 8.5 kb SacI fragment which was subcloned from phage clone P12 was selected as the DNA source for the PCR amplification. In a final volume of 50 µl, 10 pmol of dNTP mix were added to 35 ng of this DNA, and a PCR reaction was carried out in 1xPCR reaction buffer (PCR-Optimizer kit from InVitrogen) and using one unit of

10 platinum Taq DNA polymerase (from Gibco/BRL). In each case 20 pmol of the 5' and 3' primers which are defined below were added as primers. The PCR was carried out in three steps. A two-minute denaturation at 94°C was followed by 30 PCR cycles in which the DNA was first of all denaturated at 94°C for 45 sec, after which the primers were annealed, and the DNA chain was extended, at 68°C for 5 min. The

15 cycles were concluded by a chain extension at 68°C for 10 min. The selected 3' PCR primer was in each case the primer PK-3A (5'-GCAAGCTTGACGCAGCGCTGCCTGAAACTCG-3', position -43 to -65), which primer recognizes a sequence region 42 bp upstream of the ATG START codon. A promoter fragment of 4051 bp in size (NPK8) was amplified by combining

20 the PK-3A primers with the 5' PCR primer PK-5B (5'-CCAGATCTCTGGAACACAGAGTGGCAGTTTCC-3', position -4093 to -4070). Combining the pair of primers PK-3A and PK-5C (5'-CCAGATCTGCATGAAGTGTGTGGGATTTCAG-3', position -3120 to -3096) led to the amplification of a promoter fragment of 3078 bp in size (NPK15).

25 Use of the primer combination PK-3A and PK-5D (5'-GGAGATCTGATCTTGGCTTACTGCAGCCTCTG-3', position -2110 to -2087) amplified a promoter fragment of 2068 bp in size (NPK22). Finally, using the primer combination PK-3A and PK-5E

30 (5'-GGAGATCTGTCTGGATTTCCTGGGAAGTCCTCA-3', position -1125 to -1102) led to the amplification of a promoter fragment of 1083 bp in size (NPK27).

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The PK-3A primer contains a HindIII recognition sequence. The different 5' primers contain a BglII recognition sequence.

5 The resulting PCR products were purified using the Qiagen QIA quick spin PCR purification kit, in accordance with the manufacturer's instructions, and then digested with the restriction enzymes BglII and HindIII. The pGL2 promoter vector was digested with the same restriction enzymes, and the SV40 promoter contained in this vector was released and removed. The PCR promoter fragments ligated into the vector, which was then transformed into competent DH5 α bacteria (from
10 Gibco/BRL). DNA for the promoter activity analyses, which are described below, was isolated from transformed bacterial clones using the Qiagen plasmid kit.

Example 10

15 The activity of the hTC promoter was analysed in transient transfections in eukaryotic cells.

All the work with eukaryotic cells was carried out at a sterile workstation. CHO-K1 and HEK 293 cells were obtained from the American Type Culture collection.

20

CHO-K1 cells were kept in DMEM Nut Mix F-12 cell culture medium (from Gibco-BRL, order number: 21331-020) containing 0.15% streptomycin/penicillin, 2 mM glutamine and 10% FCS (from Gibco-BRL).

25 HEK 293 cells were cultured in DMOD cell culture medium (from Gibco-BRL, order number: 41965-039) containing 0.15% streptomycin/penicillin, 2 mM glutamine and 10% FCS (from Gibco-BRL).

30 CHO-K1 and HEK 293 cells were cultured at 37°C in a water-saturated atmosphere while being gassed with 5% CO₂. When the cell lawn was confluent, the medium was sucked off, after which the cells were washed with PBS (100 mM KH₂PO₄ pH

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7.2; 150 mM NaCl) and released by adding a trypsin-EDTA solution (from Gibco-BRL). The trypsin was inactivated by adding medium and the cell count was determined using a Neubauer counting chamber in order to plate out the cells at the desired density.

5

For the transfection, in each case 2×10^5 HEK 293 cells were plated out, per well, in a 24-well cell culture plate. The HEK 293 medium was removed after 3 hours. For the transfection, up to 2.5 μ g of plasmid DNA, 1 μ g of a CMV β -Gal plasmid construct (from Stratagene, order number: 200388), 200 μ l of serum-free medium and 10 μ l of transfection reagent (DOTAP from Boehringer Mannheim) were incubated at room temperature for 15 minutes and then dropped uniformly onto the HEK 293 cells. 1.5 ml of medium were added after 3 hours. The medium was changed after 20 hours. After a further 24 hours, the cells were harvested for determining the luciferase activity and the β -Gal activity. For this, the cells were lysed, at room temperature for 15 minutes, in the cell culture lysis reagent (25 mM Tris [pH 7.8] containing H_3PO_4 ; 2 mM CDTA; 2 mM DTT; 10% glycerol; 1% Triton X-100). Twenty μ l of this cell lysate were mixed with 100 μ l of luciferase assay buffer (20 mM Tricin; 1.07 mM $(MgCO_3)_4$ $Mg(OH)_2 \cdot 5H_2O$; 2.67 mM $MgSO_4$; 0.1 mM EDTA; 33.3 mM DTT; 270 μ M coenzyme A; 470 μ M luciferin, 530 μ M ATP), and the light generated by the luciferase was measured.

20

In order to measure the β -galactosidase activity, equal quantities of cell lysate and β -galactosidase assay buffer (100 mM sodium phosphate buffer, pH 7.3; 1 mM $MgCl_2$; 50 mM β -mercaptoethanol; 0.665 mg of ONPG/ml) were incubated at 37°C for at least 30 minutes or until a slight yellow coloration appeared. The reaction was stopped by adding 100 μ l of 1 M Na_2CO_3 , and the absorption was determined at 420 nm.

25

In order to analyse the hTC promoter, four hTC promoter sequence segments of differing length were cloned 5' in front of the luciferase reporter gene (cf. Example 9).

30

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The relative luciferase activities of two independent transfections in HEK 293 cells, using the constructs NPK8, NPK15, NPK22 and NPK27, are plotted in Fig. 11. Each experiment was carried out in duplicate. The standard deviation has also been given.

- 5 The construct NPK 27 exhibits a luciferase activity which is 40 times higher than the basal activity of the promoterless luciferase control construct (pGL2-basic) and from 2 to 3 times higher than that of the SV40 promoter control construct (pGL2PRO). Interestingly, a luciferase activity which was from 2 to 3 times lower than that obtained with the NPK 27 construct was observed in cells which were transfected
- 10 with longer hTC promoter constructs (NPK8, NPK15, NPK22). Similar results were also observed in CHO cells (data not shown).
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	tgatgcgttt	gtgttcagcc	actaagctgc	agtgttctgt	cacagcagca	aatgggaatag	3120
25	cagtacaggg	aatgaatac	agggacagtt	ctcagagtga	ctctcagccc	acccctggg	3179

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Patent Claims

1. Regulatory DNA sequences for the gene for the human catalytic telomerase subunit.
5
2. DNA sequences according to Claim 1, characterized in that the sequences are intron sequences in accordance with SEQ ID NO 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19 and/or 20 or fragments of these sequences which have a regulatory effect.
10
3. DNA sequences according to Claim 1, characterized in that the sequences are the 5'-flanking regulatory DNA sequence for the gene for the human catalytic telomerase subunit as depicted in Fig. 10 (SEQ ID NO 3), or fragments of this DNA sequence which have a regulatory effect.
15
4. Recombinant construct which contains a DNA sequence according to one of Claims 1 to 3.
5. Recombinant construct according to Claim 4, characterized in that it additionally contains one or more DNA sequences which encode polypeptides or proteins.
20
6. Vector which contains a recombinant construct according to Claim 4 or 5.
- 25 7. Use of recombinant constructs or vectors according to one of Claims 4 to 6 for preparing medicaments.
8. Recombinant host cells which harbour recombinant constructs or vectors according to one of Claims 4 to 6.
30

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9. Process for identifying substances which affect the promoter activity, silencer activity or enhancer activity of the human catalytic telomerase subunit, comprising the following steps:
- 5 A. adding a candidate substance to a host cell which harbours DNA sequences according to one of Claims 1 to 3, which sequences are functionally linked to a reporter gene, and
- B. measuring the effect of the substance on expression of the reporter gene.
- 10
10. Process for identifying factors which bind specifically to the DNA according to one of Claims 1 to 3, or to fragments thereof, characterized in that an expression cDNA library is screened using a DNA sequence according to one
- 15 of Claims 1 to 3, or subfragments of widely differing length, as the probe.
11. Transgenic animals which harbour recombinant constructs or vectors according to Claims 4 to 6.
- 20 12. Process for detecting telomerase-associated conditions in a patient, comprising the following steps:
- A. incubating a recombinant construct or vector according to Claims 4 to 6, which additionally contains a reporter gene, with body fluids or cell
- 25 samples,
- B. detecting the activity of the reporter gene in order to obtain a diagnostic value, and

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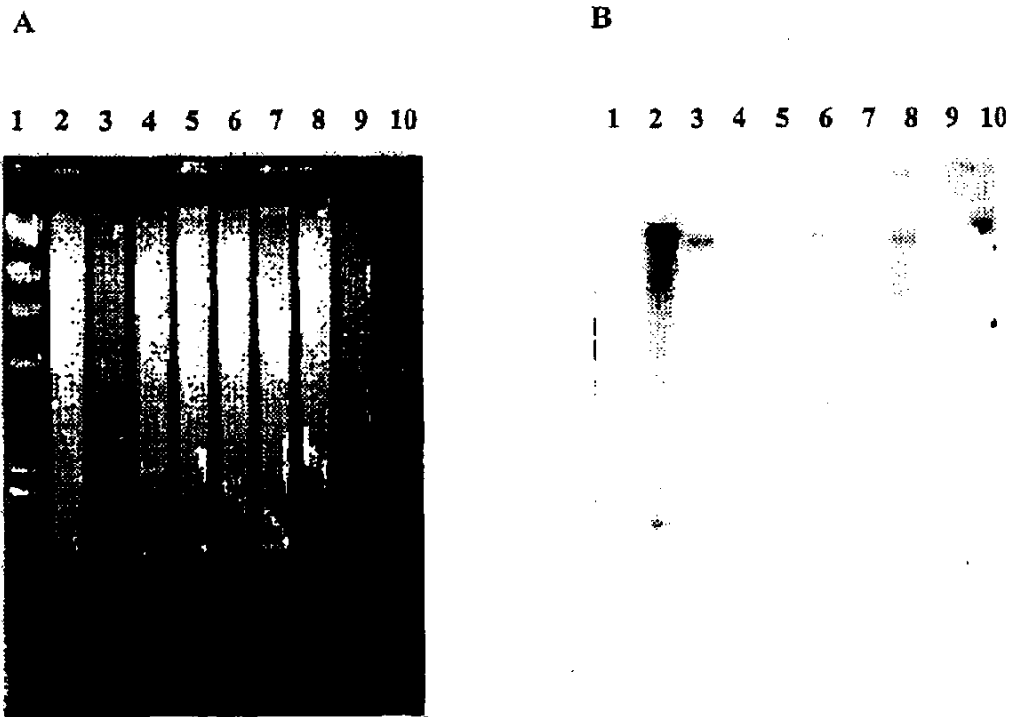
- C. comparing the diagnostic value with standard values for the reporter gene construct in standardized normal cells or body fluids of the same type as the test sample.

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Fig. 1

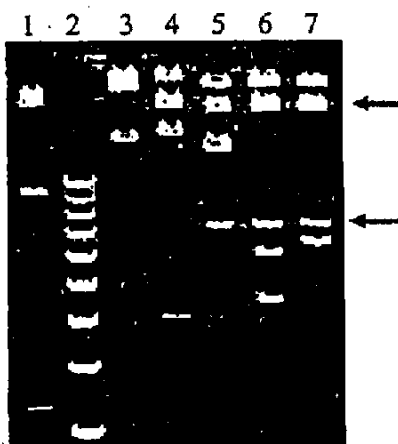


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Fig. 2



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Fig. 3

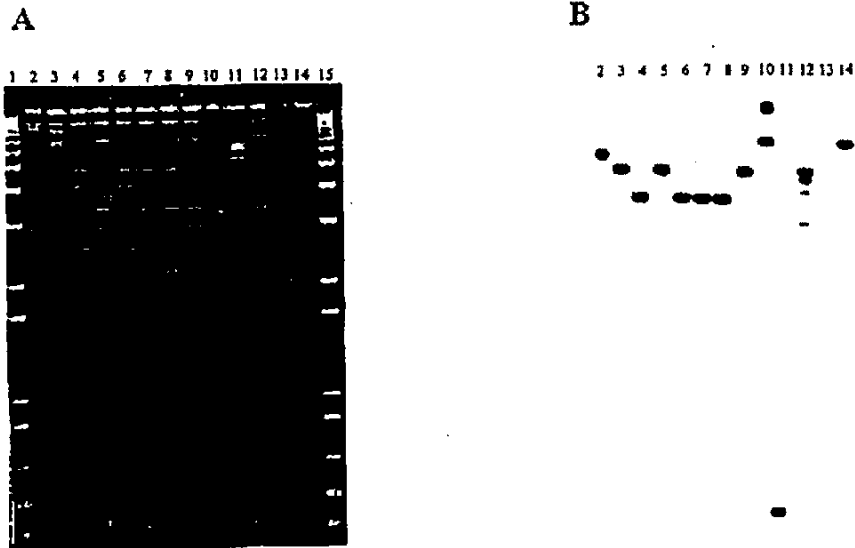


Fig. 4

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Fig. 4 (Fortsetzung)

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Fig. 5

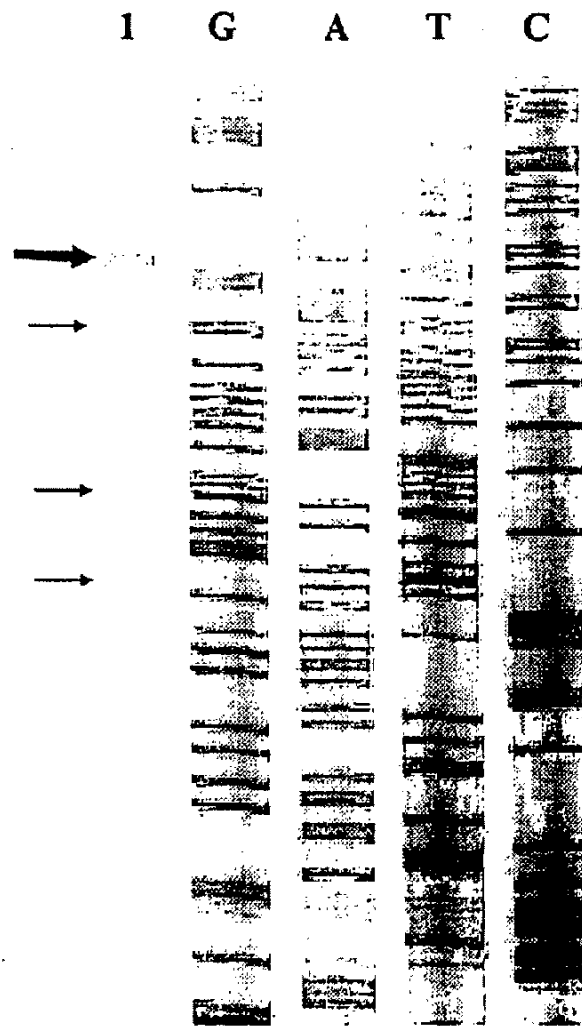


Fig. 6

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Fig. 7

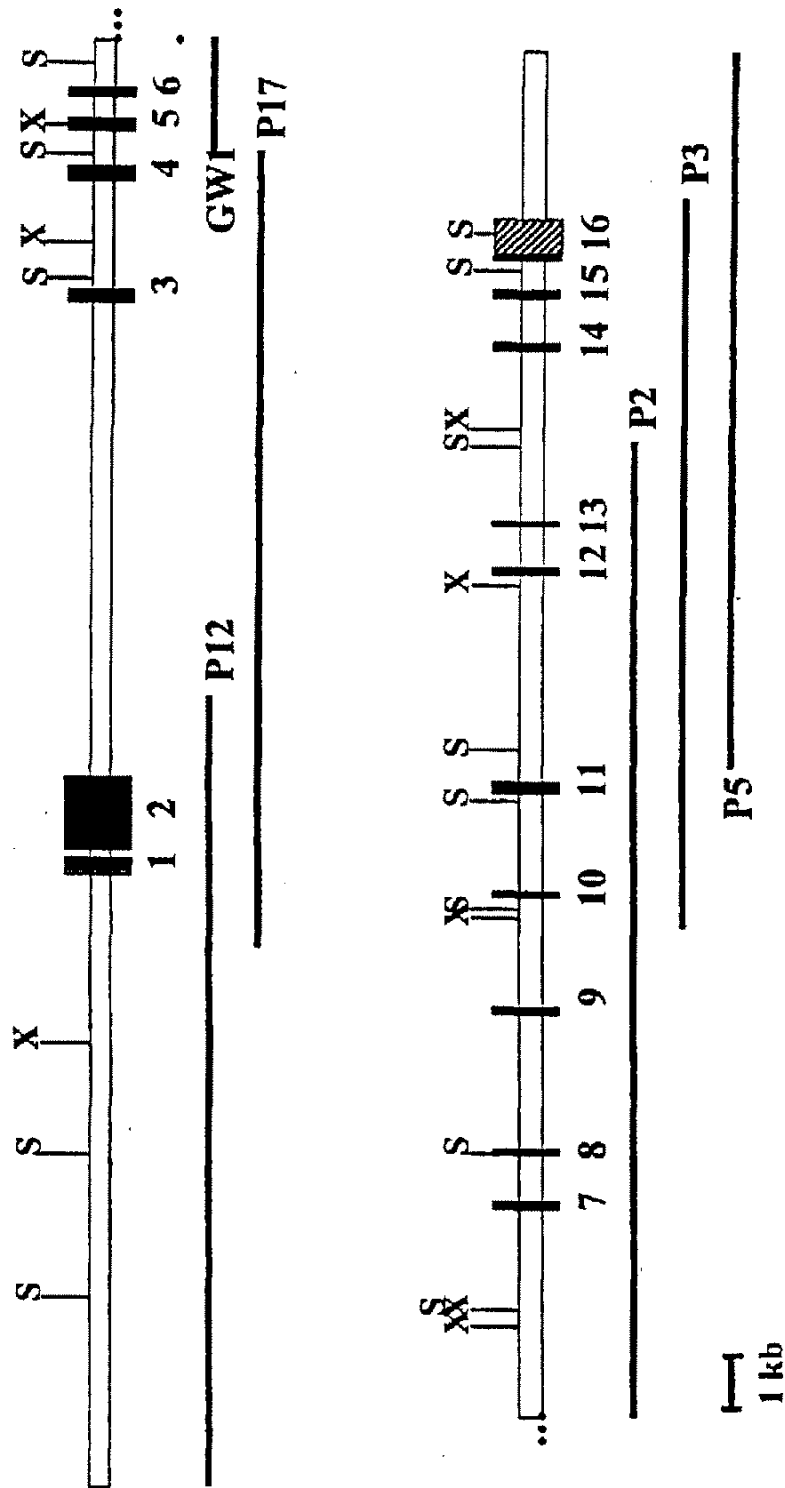


Fig. 8A

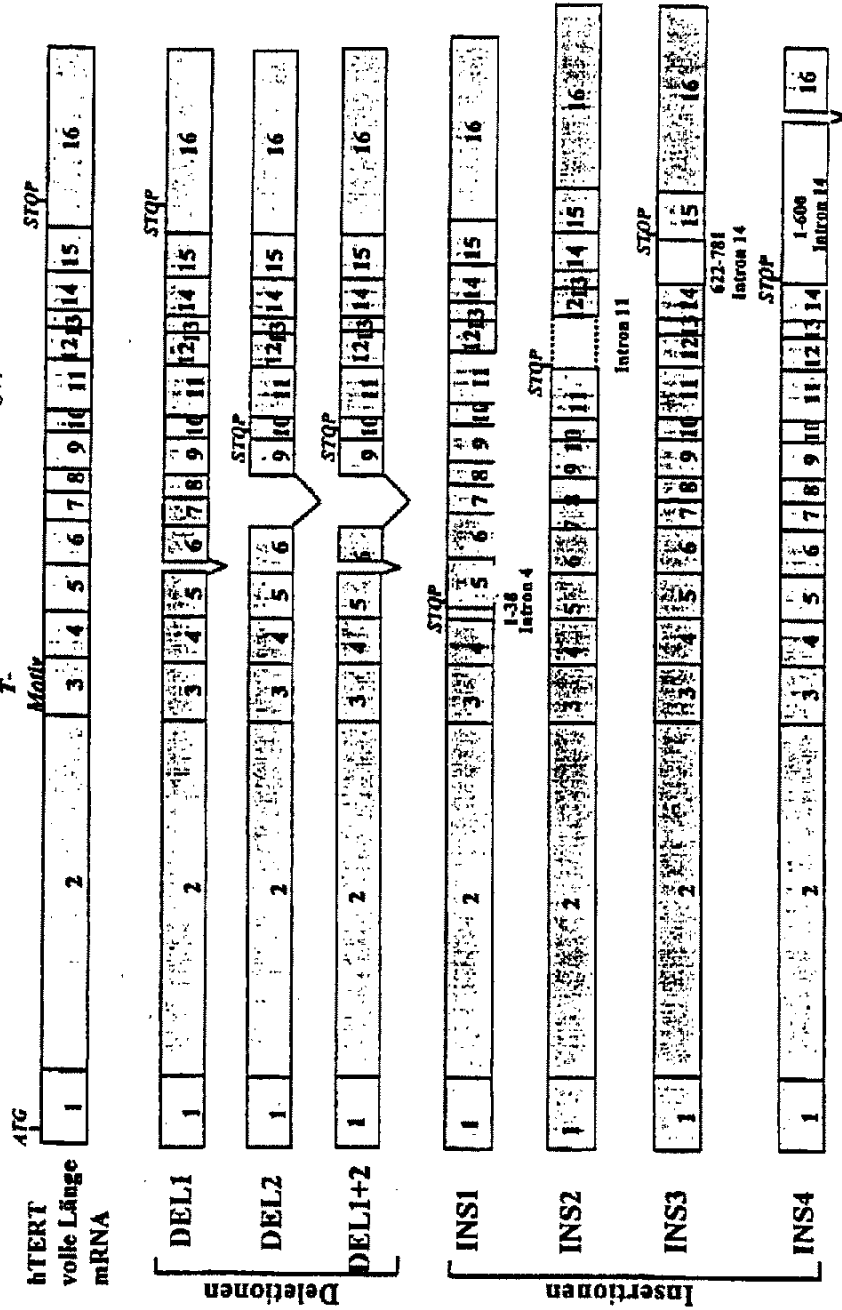
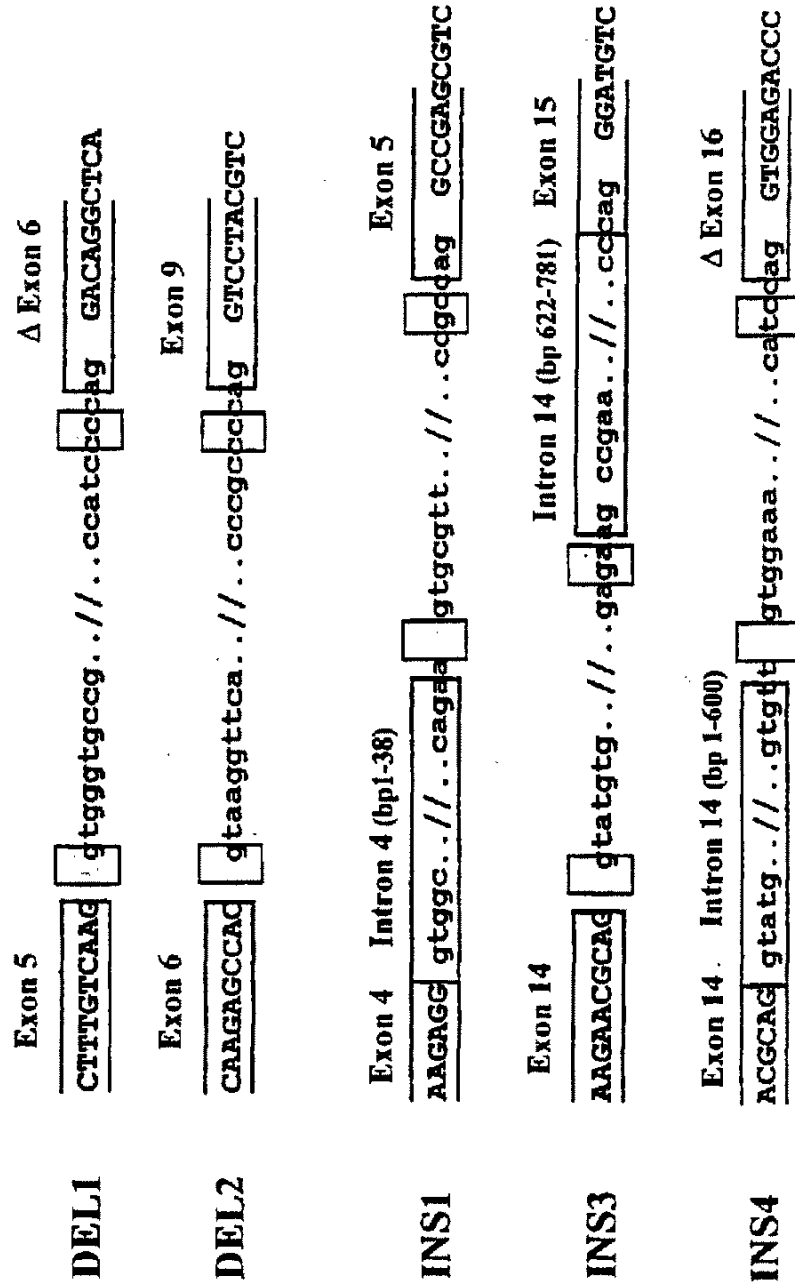


Fig. 8B



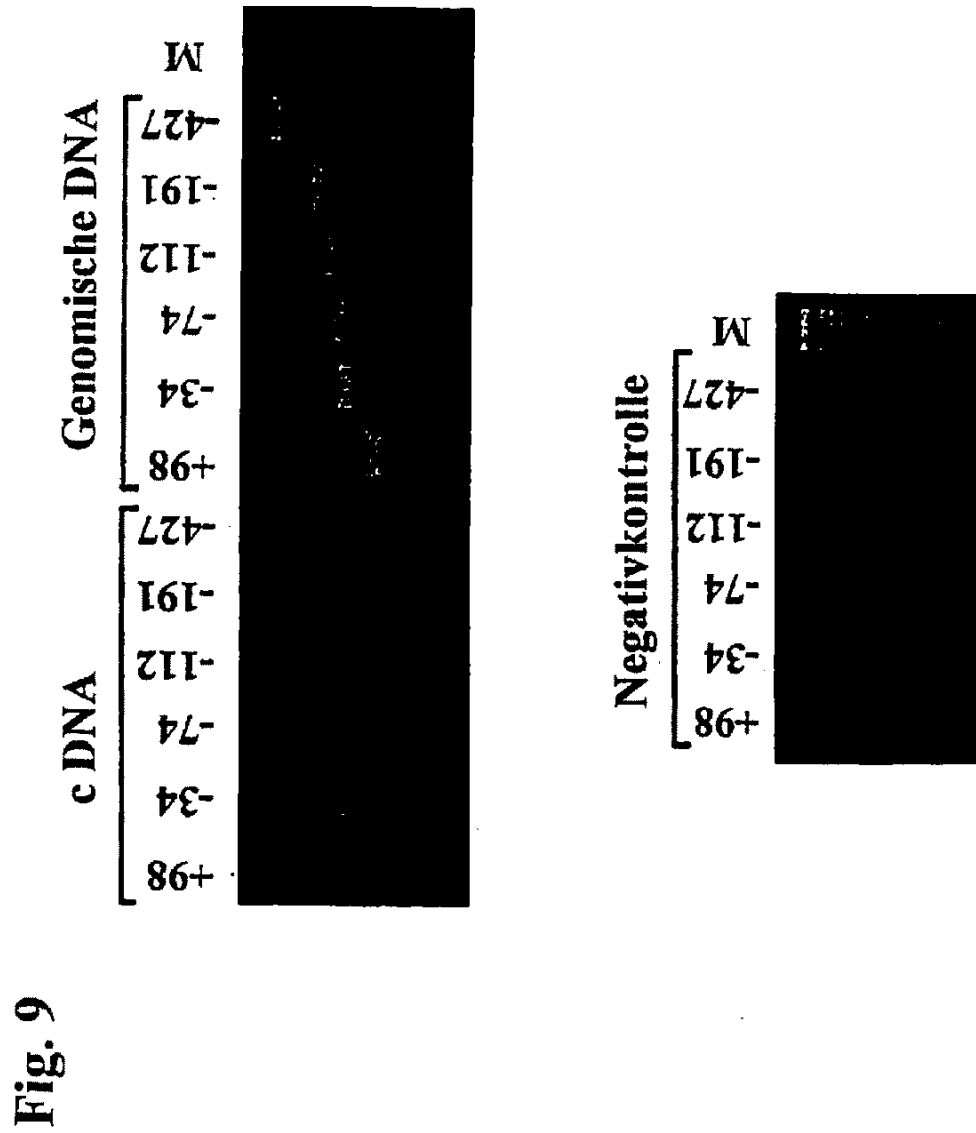


Fig. 10

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 AAAGAAGAAT GAATTCCTAAT CCTACTCAA CTATTCTGAA AAATAGAGGA AAGAATACTT CCAAACTCAT -10014
 TCTACATGGC CAGTATTACC CTGATTCCAA AACCAGACAA AAACACATCA AAAACAAACA AACAAAAAAA -9944
 CAGAAAGAAA GAAACTTACA GGCCAATATC CTTGATGAAT ACTGATACAA AAATCCTCAA CAAAACACTA -9874
 GCAAACCAA TTAACAACA CCTTCGAAAG ATCATTCAAT GTGATCAAGT GGGATTTATT CCAGGGATGG -9804
 AAGGATGGTT CAACATATGC AAATCAATCA ATGTGATACA TCATCCCAAC AAAATGAAGT ACAAAAATA -9734
 TATGATTATT TCACTTTATG CAGAAAAAGC ATTTGATAAA ATTCTGCACC CTTCTAGATA AAAACCCCTA -9664
 AAAAACCAGG TATACAGAA ACATACAGGC CAGGCACAGT GGCTCACACC TGCATGCCCA GCACCTGGG -9594
 AGGCCAAGT GGGATGATTG CTTGGGCCCA GGAGTTGAG ACTAGCCTGG GCAACAAAAT GAGACCTGGT -9524
 CTACAAAAAA CTTTTTAAA AAATTAGCCA GGCATGTGG CATATGCCTG TAGTCCAGC TAGTCTGGAG -9454
 GCTGAGGTGG GAGAATCACT TAAGCCTAGG AGGTCGAGGC TGCAGTGAGC CATGAACATG TCACTGTACT -9384
 CCAGCCTAGA CAACAGAAC AGACCCCACT GAATAAGAG AGGAGAAGG AGAAGGGAGA AGGGAGGGAG -9314
 AAGGAGGAG GAGGAGAAG AGGAGGTGGA GGAGAAGTG AAGGGGAAG GGAAGGGAAA GAGGAGAAG -9244
 AAGAAACATA TTGACATA ATAAGGCC TATATGACAG ACCGAGTAG TATTATGAGG AAAAAGTAA -9174
 AGCCTTTTCT CTAAGATCTG GAAAATGACA AGGGCCCACT TTCACCACTG TGATTCAACA TAGTACTAGA -9104
 AGTCTTAGCT AGAGCAATCA GATAAGAGAA AGAAATAAA GGCATCCAAA CTGGAAAGGA AGAAGTCAA -9034
 TTATCTGTT TGCAGATGAT ATGATCTTAT ATCTGGAAA GACTTAAGAC ACCACTAAAA AACTATTAGA -8964
 GCTGAAATTT GGTACAGCAG GATACAAAT CAATGTACAA AAATCAGTAG TATTTCTATA TTCCAACAGC -8894
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 GTGAAAGATC TCTACAATGA AAATATAAA ATGTTGATAA AAGAAATTGA AGAGGGCACA AAAAAGAAA -8754
 AGATATTCCA TGTTCTAGA TTGGAAGAT AAATACTGTT AAATATGTTA TACTACCCAA AGCAATTTAC -8684
 AAATTCATG CAATCCCTAT TAAATACTA ATGACGTTCT TCACAGAAAT AGAAGAAACA ATTCTAAGAT -8614
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 TTTTGTACAA AGGTGCCAAG AACATACTTT GGGGAAAAGA TAATCTCTTC AATAAATGGT GCTGGAGGAA -8334
 CTGGATATCC ATATGCAAAA TAACAATACT AGAATCTGT CTCTCACCAT ATACAAAAGC AAATCAAAAT -8264
 GGTGAAAGG CTTAAATCTA AAACCTCAA CTTTGCAACT ACTAAAAGAA AACACCGGAG AAATCTCCA -8194
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 TGCAGCACTG TTCATAGCAG CCAAGGTTTG GAAGCAACCT CAGTGTCCAT CAACAGACGA ATGGAAAAAG -7494
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 TTGCTTAAAC CTGGGAGCGG GAGGTTGCG TGAGCCGAGC TCATGCCACT GCACTGCAGC CTGGGTGACA -6794
 GAGCAAGACT CCATCTCAA ACAAACAA AAAAAGAAG ATTAATAATG TAATTTTAT GTACCGTATA -6724
 AATATATACT CTACTATATT AGAAGTTAAA AATTAACA ATTATAAAG GTAATTAACT ACTTAATCTA -6654
 AAATAAGAAC AATGTATGTG GGTTTCTAG CTCTGAAGA AGTAAAGTT ATGGCCACGA TGGCAGAAAT -6584

Fig. 10

GTGAGGAGGG AACAGTGGAA GTTACTGTTC TTAGACGCTC ATACTCTCTG TAAGTGACTT AATTTTAACC -6514
 AAAGACAGGC TGGGAGAAGT TAAAGAGGCA TTCTATAAGC CCTAAAACAA CTGCTAATAA TGGTGAAGG -6444
 TAATCTCTAT TAATTACCAA TAATTACAGA TATCTCTAAA ATCGAGCTGC AGAATTGGCA CGTCTGATCA -6374
 CACCGTCTCT TCATTACCGG TGCTTTTTTT CTGTGTGCT TGGAGATTTT CGATTGTGTG TTCGTGTTTG -6304
 GTTAACTTA ATCTGTATGA ATCTGAAAC GAAAAATGGT GGTGATTTC TCCAGAAGAA TTAGAGTACC -6234
 TGGCAGGAAG CAGGTGGCTC TGTGGACCTG AGCCACTTCA ATCTTCAAGG GTCTCTGGCC AAGACCCAGG -6164
 TGCAAGGCAG AGGCCTGATC ACCCGAGGAC AGGAAAGCTC GGATGGGAAG GGGCGATGAG AAGCCTGCCT -6094
 CGTTGGTGAG CAGCCATGA AGTGCCCTTA TTACGCTTT TTTACGCTTT GCAAGATTG CTCTGGATAC CATCTGGAAA -6024
 AGGCGGCCAG CGGGAATGCA AGGAGTCAGA AGCCTCCTGC TCAAACCCAG GCCAGCAGCT ATGGCGCCCA -5954
 CCCGGGCGTG TGCCAGAGGG AGAGGAGTCA AGGCACCTCG AAGTATGGCT TAAATCTTTT TTTCACCTGA -5884
 AGCAGTGACC AAGGTGTATT CTGAGGGAAG CTTGAGTTAG GTGCCCTCTT TAAACAGAA AGTCATGGAA -5814
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 CCCTCGCGGT TTCTGATCGG GACAGAGTGA CCCCCGTGGA GCTTCTCCGA GCCCGTGTG AGGACCCCTC -5674
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 GTGACTCAGG ACCCATACCC GGCTTCTCTG GCCCACCACG ACTAACCAG GAAATCACGG AGCTCTGAAC -5114
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 CCTGGCCTCC GGCTGCACGC TGACCTCCAT TTCAGGCGC TCCCGTCTC CTGTCTCTG CCGGGGCTG -4344
 CCGGTGTGTT CTCTGTCTT TGTGCTCCTT TCCACGTCCA GCTGCGTGTG TCTCTGCCCG CTAGGGTCTC -4274
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 ACTAAGCATC CTCTTCCCAA AAGACCCAGC ATTTGGACCC CTGGACATT GCCCCACAGC CCTGGGAATT -3994

cdm
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 CAAGCAGGGG AAATCCCTGC TAAATGTCC TTTAACAAAC TGTTAAACA AACGGGTCCA TCCGCACGGT -3854
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 GCTTACTGCA GCCTCTGCCT CCCAGGTTCA AGTGATTCTC CTGCTTCCGC CTCCCATTTG GCTGGGATTA -2034
 CAGGCACCCG CCACCATGCC CAGCTAATTT TTTGTATTT TAGTAGAGAC GGGGGTGGGT GGGGTTCCAC -1964

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Fig. 10

ATGTTGGCCA GGCTGGTCTC GAACTTCTGA CCTCAGATGA TCCACCTGCC TCTGCCTCCT AAAGTGCTGG -1894
 GATTACAGGT GTGAGCCACC ATGCCCAGCT CAGAATTTAC TCTGTTTAGA AACATCTGGG TCTGAGGTAG -1824
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 CTCTTGATGT TTTACACTGT GATGACTAAG ACATCATCAG CTTTCAAAG ACACACTAAC TGCACCCATA -1684
 ATACTGGGGT GTCTTCTGGG TATCAGCAAT CTTCAATTGA TGCCGGGAGG CGTTTCTCG CCATGCACAT -1614
 GGTGTTAAT ACTCCAGCAT AATCTTCTGC TTCCATTTCT TCTCTTCCCT CTTTTAAAT TGTGTTTTCT -1544
 ATGTTGGCTT CTCTGCAGAG AACCAGTGTA AGCTACAAT TAACTTTTGT TGAACAAAT TTTCCAACC -1474
Sp1
GCCCCTTTGC CCTAGTGGCA GAGACAATTC ACAAACACAG CCCTTTAAAA AGGCTTAGGG ATCACTAAGG -1404
 GGATTTCTAG AAGAGCGACC TGTAATCCTA AGTATTTACA AGACGAGGCT AACCTCCAGC GAGCGTGACA -1334
 GCCCAGGGAG GGTGCGAGGC CTGTTCAAAT GCTAGCTCCA TAAATAAAGC AATTTCTCTC GGCAGTTTCT -1264
 GAAAGTAGGA AAGGTTACAT TTAAGGTTGC GTTTGTTAGC ATTTCACTGT TTGCCGACCT CAGCTACAGC -1194
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 GCGCCTGGCT CCATTCCCA CCGTTCTCG ACGGGACCGC CCGGTGGGT GATTACAGA TTTGGGGTGG -774
 TTTGCTCATG GTGGGGACCC CTCGCCCT GAGAACCTGC AAGAGAAAT GACGGGCCTG TGTCAAGGAG -704
 CCCAAGTCGC GGGGAAGTGT TGCAGGAGG CACTCCGGGA GGTCCCGCT GCGCTCCAG GGAGCAATGC -634
 GTCCTCGGGT TCGTCCCCAG CCGCTCTAC GCGCTCCGT CCTCCCTTC ACGTCCGGCA TTCGTGGTGC -564
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 GCGGATTGCA CCTCTCTCCG CTGGGGCCCT CGCTGGCGTC CCTGCACCCT GGGAGCGCGA GCGGCGCGCG -354
GCGCGGGAAG CGCGGCCAG ACCCCCGGT CCGCCGGAG CAGCTGCGCT GTCGGGGCCA GGCCGGGCTC -284
 CCAGTGGATT CGCGGGCACA GACGCCCAGG ACCGCGCTCC CCACGTGCG GAGGGACTGG GGACCCGGGC -214
 ACCCGTCTG CCCCTTACC TTCCAGCTCC GCCTCTCCG CGCGGACCC GCCCGGTCCC GACCCCTCCC -144
 GGGTCCCCG CCCAGCCCC TCCGGGCCCT CCCAGCCCT CCCCTTCTT TCCGCGGC CGCCCTCTCC -74
 TCGCGCGCG AGTTTCAGGC AGCGCTGCGT CCTGCTGCG ACGTGGGAAG CCCTGGCCCC GGCCACCCCC -4
 GCGATG

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